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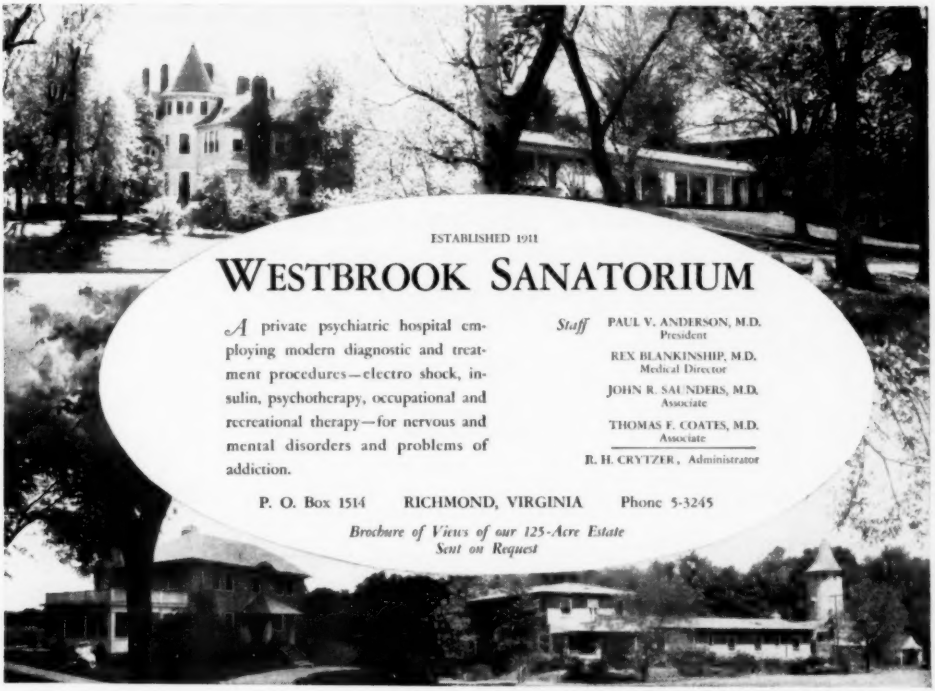

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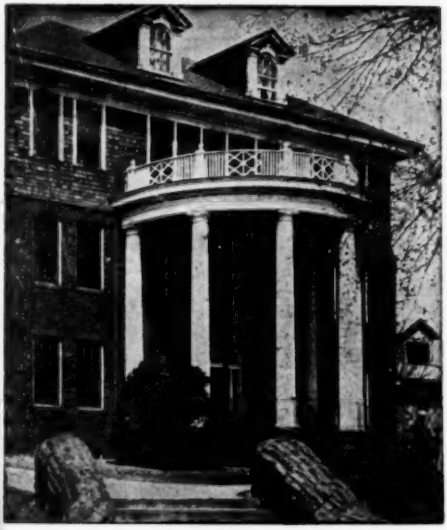

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VOLUME 68 AUGUST 1952 NUMBER 2

COPYRIGHT, 1952, BY THE AMERICAN MEDICAL ASSOCIATION

INFLUENCE OF CHANGES IN CEREBRAL BLOOD FLOW ON THE CEREBROSPINAL FLUID PRESSURE

HENRY W. RYDER, M.D.
FRANK F. ESPEY, M.D.
FARISS D. KIMBELL, M.D.
LIEUTENANT (jg) ERNEST J. PENKA (MC), U.S.N.
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JOSEPH P. EVANS, M.D.
With the Technical Assistance of Doris Lamb, Edythe Barnes, Joan Jackson, and William Brosene
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WE HAVE previously reported that changes in cerebral blood flow may have a profound effect in the same direction on the cerebrospinal fluid pressure of rhesus monkeys.[1] The present communication deals with this relationship in man.

MATERIAL AND METHODS

The types of patients studied and the methods of continuously recording the several pressures of interest have been described.[2] Included in this study are patients who were sufficiently cooperative to hyperventilate and lie quietly.

OBSERVATIONS

The administration of carbon dioxide in air increases the cerebral blood flow [3] and the cerebrospinal fluid pressure.[4] Hyperventilation decreases the flow [5] and the

This investigation was financed by a grant from the Department of the Army.

Neurosurgical Fellow, assigned by the Navy Department to the University of Cincinnati (Lieut. Penka). Fellow of the Rockefeller Foundation (Dr. Rosenauer). Consultant Physicist (Dr. Podolsky). Research Engineer, Lederle Laboratories Division, American Cyanamid Company (Mr. Brosene).

From the Department of Surgery, Division of Neurosurgery, University of Cincinnati College of Medicine.

1. Ryder, H. W.; Espey, F. F.; Kristoff, F. V., and Evans, J. P.: Observations on the Interrelationships of Intracranial Pressure and Cerebral Blood Flow, J. Neurosurg. **8**:46-58, 1951.

2. Ryder, H. W.; Espey, F. F.; Kimbell, F. D.; Penka, E. J.; Rosenauer, A.; Podolsky, B., and Evans, J. P.: Mechanism of the Change in Cerebrospinal Fluid Pressure Following an Induced Change in the Volume of the Fluid Space, unpublished study.

3. Kety, S. S., and Schmidt, C. F.: Effects of Altered Arterial Tension of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, J. Clin. Invest. **27**:484-492, 1948.

(Footnotes continued on next page)

fluid pressure.[4] The cerebrospinal fluid pulse pressure varies concomitantly with the irregular arterial pulses of auricular fibrillation and extrasystoles. These procedures and conditions usually cause concomitant changes in the arterial pressure in the same direction, which have been assumed by other investigators to be the causative mechanism, in whole or in part, for the changes in cerebrospinal fluid pressure.

To show that it is the flow rather than the concomitant variations in arterial pressure which is responsible for the effects, it is necessary to modify the flow and arterial pressure in opposite directions simultaneously and to observe that the

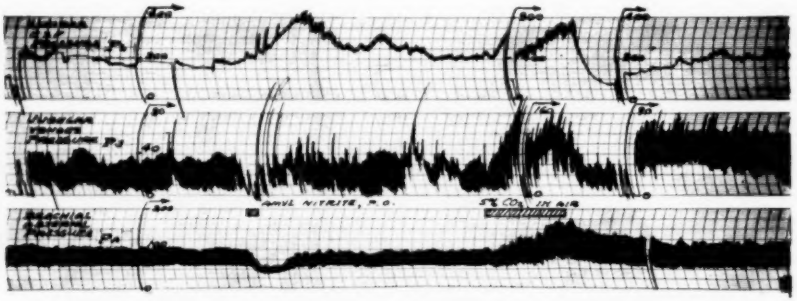

Fig. 1.—The tracings are from the record of a man aged 36 who was running a cerebrospinal fluid pressure of 200 mm. of water because of a chronic subdural hematoma. The hematoma was removed two weeks after the recording was made. The extraordinarily wide jugular venous pulses were due to insufficiency of the tricuspid valve following a healed rheumatic lesion. The unusual abrupt drop in fluid pressure after discontinuation of the administration of carbon dioxide is considered to have been due to his continuing to hyperventilate after the removal of the chemical stimulus.

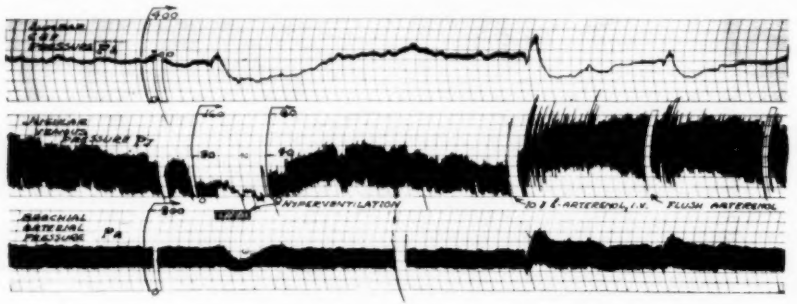

Fig. 2.—The continuously recorded pressures immediately follow those of Figure 1.

responses in cerebrospinal fluid pressure follow the flow rather than the arterial pressure. We think this occurs after the brief administration of amyl nitrite and arterenol,[6] for example, although we cannot measure transient changes in flow quan-

4. Cobb, S., and Fremont-Smith, F.: The Cerebral Circulation: Changes in the Human Retinal Circulation and in the Pressure of the Cerebrospinal Fluid During Inhalation of a Mixture of Carbon Dioxide and Oxygen, Arch. Neurol. & Psychiat. **26**:731-736, 1931.

5. Kety, S. S., and Schmidt, C. F.: Effects of Active and Passive Hyperventilation on Cerebral Blood Flow, Cerebral Oxygen Consumption, Cardiac Output, and Blood Pressure of Normal Young Men, J. Clin. Invest. **25**:107-119, 1946.

6. Dr. Arnold Iglauer supplied the *l*-arterenol.

TABLE 1.—*Comparative Effects of Inhalation of Carbon Dioxide and Amyl Nitrite on Mean Pressures in Cerebrospinal Fluid, Jugular Vein, and Brachial Artery**

Patient; Sex; Age; Diagnosis		5+% Carbon Dioxide			Amyl Nitrite				
		t_0	t_1	t_1-t_0	t_0	t_1	t_2	t_1-t_0	t_2-t_0
Alex; M; 60; herniated intervertebral disk	P_F	190	600	410	175	230	300	55	125
	P_J	140	250	110	160	190	200	30	40
	P_A	97	133	36	107	73	95	−34	−12
	$P_F - P_J$	50	350	300	15	40	100	25	85
Ande; M; 74; chronic subdural hematoma	P_F	170	460	290	175	220	270	45	95
	P_J	50	120	70	50	45	50	−5	0
	P_A	88	110	22	95	78	82	−17	−13
	$P_F - P_J$	120	340	220	125	175	220	50	95
Ande; M; 74; chronic subdural hematoma	P_F	120	400	280	210	275	375	65	165
	P_J	90	100	10	225	300	350	75	125
	P_A	128	170	42	145	97	127	−48	−18
	$P_F - P_J$	30	300	270	−15	−25	25	−10	40
Coll; F; 37; hemorrhage of right middle cerebral artery	P_F	145	430	285	110	135	280	25	180
	P_J	100	170	70	75	75	90	0	15
	P_A	85	97	12	85	58	78	−27	−7
	$P_F - P_J$	45	260	215	35	60	200	25	165
Fiel; M; 40; post-traumatic epilepsy	P_F	250	850	600	200	225	440	25	240
	P_J	125	155	30	135	125	135	−10	0
	P_A	90	117	27	92	73	92	−19	0
	$P_F - P_J$	125	695	570	65	100	305	35	240
Gask; M; 21; brain tumor	P_F	195	230	35	185	215	375	30	190
	P_J	120	120	0	100	115	125	15	25
	P_A	73	77	4	73	35	63	−38	−10
	$P_F - P_J$	75	110	35	85	100	250	15	165
Gask; M; 21; brain tumor	P_F	330	550	220	350	425	525	75	175
	P_J	40	70	30	35	45	50	10	15
	P_A	87	103	16	82	67	77	−15	−5
	$P_F - P_J$	290	480	190	315	380	475	65	160
Haze; M; 22; cerebral contusion	P_F	120	460	340	125	215	325	90	200
	P_J	50	110	60	80	60	50	−20	−30
	P_A	102	107	5	122	65	93	−57	−29
	$P_F - P_J$	70	350	280	45	155	275	110	230
Henr; M; 61; brain tumor	P_F	55	100	45	40	150	245	110	205
	P_J	22	65	43	17	45	40	28	23
	P_A	100	115	15	95	40	90	−55	−5
	$P_F - P_J$	33	35	2	23	105	205	82	182
Jame; F; 45; metastatic neoplasm to skull	P_F	230	1,000	770	400	420	830	20	430
	P_J	55	150	95	45	50	55	5	10
	P_A	102	123	21	103	65	103	−38	0
	$P_F - P_J$	175	850	675	355	370	775	15	420
Kunk; M; 50; bilateral subdural hematoma	P_F	200	230	30	160	200	350	40	190
	P_J	130	130	0	100	120	150	20	50
	P_A	112	118	6	110	60	103	−50	−7
	$P_F - P_J$	70	100	30	60	80	200	20	140
Mont; M; 27; chronic subdural hematoma	P_F	250	370	120	140	270	425	130	285
	P_J	70	120	50	65	70	75	5	10
	P_A	122	140	18	110	75	110	−35	0
	$P_F - P_J$	180	250	70	75	200	350	125	275
Morg; M; 31; cerebral contusion	P_F	130	330	200	140	220	320	80	180
	P_J	150	120	−30	145	145	180	0	35
	P_A	93	105	12	95	67	77	−28	−18
	$P_F - P_J$	−20	210	230	−5	75	140	80	145
McGu; M; 37; paresis	P_F	70	150	80	95	180	230	85	135
	P_J	70	115	45	125	180	230	55	105
	P_A	100	113	13	112	67	92	−45	−20
	$P_F - P_J$	0	35	35	−30	0	0	30	30
Neel; M; 26; chronic subdural hematoma	P_F	225	330	105	200	320	360	120	160
	P_J	35	45	10	35	40	35	5	0
	P_A	92	117	25	90	70	75	−20	−15
	$P_F - P_J$	190	285	95	165	280	325	115	160
Peni; M; 45; cerebral contusion	P_F	150	800	650	190	270	430	80	240
	P_J	85	110	25	100	115	125	15	25
	P_A	92	113	21	93	78	92	−15	−1
	$P_F - P_J$	65	690	625	90	155	305	65	215
Scot; M; 38; hemorrhage left middle central artery	P_F	110	250	140	125	175	190	50	65
	P_J	120	175	55	100	150	155	50	55
	P_A	102	127	25	102	82	87	−20	−15
	$P_F - P_J$	−10	75	85	25	25	35	0	10
Slau; M; 56; epilepsy	P_F	120	190	70	125	275	460	150	335
	P_J	40	35	−5	40	60	60	20	20
	P_A	90	93	−3	92	67	118	−25	26
	$P_F - P_J$	80	155	75	85	215	400	130	315
Stev; M; 41; paralysis agitans	P_F	190	640	450	175	210	310	35	135
	P_J	180	260	80	190	215	230	25	40
	P_A	140	150	10	133	108	132	−25	−1
	$P_F - P_J$	10	380	370	−15	−5	80	10	95
Wood; M; 47; subdural hematoma	P_F	225	375	150	200	215	335	15	135
	P_J	130	175	45	160	135	135	−25	−25
	P_A	82	115	33	90	45	80	−45	−10
	$P_F - P_J$	95	200	105	40	80	200	40	160

* The time at the start of the procedure is indicated by t_0. With carbon dioxide, t_1 is the time when the pressure response was maximal. With amyl nitrite, t_1 is the time when the arterial pressure was minimal, and t_2 is the time when the cerebrospinal fluid pressure was maximal. P_F and P_J are the mean cerebrospinal fluid and jugular venous pressures, in millimeters of water, and P_A is the mean arterial pressure, in millimeters of mercury.

titatively. The comparative effects of amyl nitrite and carbon dioxide on the pressures are of interest. Both procedures raise the cerebrospinal fluid pressure, while the carbon dioxide raises the arterial pressure and amyl nitrite lowers it (Fig. 1; Tables

TABLE 2.—*Effect of Certain Drugs and Procedures on Cerebral Hemodynamics**

Change in Pressure	5+% Carbon Dioxide, t_1-t_0	Amyl Nitrite		Hyperventilation, t_1-t_0	Arterenol		
		t_1-t_0	t_2-t_0		t_1-t_0	t_2-t_0	t_2-t_1
Cerebrospinal pressure, mm. water	264 ± 48^3	66 ± 10^3	193 ± 19^3	-45 ± 11^3	30 ± 9^2	-27 ± 11^1	-57 ± 10^4
Jugular vein, mm. water	40 ± 8^3	15 ± 6^2	27 ± 8^3	-6 ± 23^0	16 ± 20^0	-3 ± 18^0	-19 ± 30^0
Brachial artery, mm. Hg	18 ± 3^3	-33 ± 3^4	-8 ± 3^3	-9 ± 2^3	30 ± 3^4	7 ± 3^1	-23 ± 3^4
Cerebrospinal pressure — jugular vein	224 ± 41^4	50 ± 8^3	166 ± 22^3	-39 ± 11^3	14 ± 8^0	-24 ± 16^0	-38 ± 12^2
b	0.79 ± 0.68^0	.....	0.58 ± 0.19^3	-0.45 ± 0.11^3	.....	-0.41 ± 0.27^0	.....

* The times t_0, t_1, and t_2 are those illustrated in Figures 1 and 2, at which the mean pressures were those recorded in Tables 1 and 3. The tabular values are the mean differences and their standard errors, calculated from these data. The regression coefficient, b, is the dependance of the change in relative cerebrospinal fluid pressure on the initial relative cerebrospinal fluid pressure, where the relative cerebrospinal fluid pressure is the cerebrospinal fluid pressure less the jugular venous pressure. The probability of the chance occurrence of the indicated mean deviations is given by the superscripts as follows: ^{0}, >0.05; ^{1}, $0.05-0.02$; ^{2}, $0.02-0.01$; ^{3}, $0.01-0.001$; ^{4}, <0.001.

TABLE 3.—*Comparative Effects of Arterenol and Hyperventilation on Mean Pressures in Cerebrospinal Fluid Space, Jugular Vein and Brachial Artery**

Patients; Sex; Age; Dose of Arterenol (γ); Diagnosis		Arterenol						Hyperventilation		
		t_0	t_1	t_2	t_1-t_0	t_2-t_0	t_2-t_1	t_0	t_1	t_1-t_0
Aude; M; 74; 10; chronic subdural hematoma	P_F	83	115	75	32	−8	−40	80	65	−15
	P_J	140	165	120	25	−20	−45	135	150	15
	P_A	98	125	95	27	−3	−30	110	97	−13
	$P_F - P_J$	−57	−50	−45	7	12	5	−55	−85	−30
Clea; M; 36; 10; chronic subdural hematoma	P_F	225	230	115	5	−110	−105	188	100	−88
	P_J	20	50	50	30	30	0	15	5	−10
	P_A	72	97	80	25	8	−17	77	60	−17
	$P_F - P_J$	205	170	65	−35	−140	−105	173	95	−78
Coll; F; 37; 20; right middle cerebral artery hemorrhage	P_F	120	175	125	55	5	−50	125	60	−65
	P_J	50	135	85	45	5	−50	70	40	−30
	P_A	80	100	82	20	2	−18	78	78	0
	$P_F - P_J$	30	40	40	10	10	0	55	20	−35
Fiel; M; 40; 10; post-traumatic epilepsy	P_F	190	240	150	50	−40	−90	230	140	−90
	P_J	130	170	130	40	0	−40	120	125	5
	P_A	92	135	113	43	21	−22	82	82	0
	$P_F - P_J$	60	70	20	10	−40	−50	110	15	−95
Haze; M; 22; 20; cerebral contusion	P_F	110	115	85	5	−25	−30	105	70	−35
	P_J	65	50	40	−15	−25	−10	60	35	−25
	P_A	97	128	100	31	3	−28	95	87	−8
	$P_F - P_J$	45	65	45	20	0	−20	45	35	−10
Henr; M; 61; 20 brain tumor	P_F	65	60	52	−5	−13	−8	45	50	5
	P_J	55	35	38	−20	−17	3	20	5	−15
	P_A	103	122	102	19	−1	−20	90	70	−20
	$P_F - P_J$	10	25	14	15	4	−11	25	45	20
Kayt; F; 60; 20; right middle cerebral artery hemorrhage	P_F	185	250	175	65	−10	−75	185	150	−35
	P_J	85	90	95	5	10	5	95	95	0
	P_A	77	103	90	26	13	−13	77	70	−7
	$P_F - P_J$	100	160	80	60	−20	−80	90	55	−35
Mont; M; 27; 20; chronic subdural hematoma	P_F	110	140	90	30	−20	−50	100	85	−15
	P_J	55	70	50	15	−5	−20	40	70	30
	P_A	110	153	117	43	7	−36	110	107	−3
	$P_F - P_J$	55	70	40	15	−15	−30	60	15	−45
Moor; F; 45; 20; cerebral contusion	P_F	130	170	105	40	−25	−65	140	70	−70
	P_J	38	53	42	15	4	−11	57	30	−27
	P_A	83	120	92	37	9	−28	92	78	−14
	$P_F - P_J$	92	117	63	25	−29	−54	83	40	−43

* The time when the procedure was started is indicated by t_0. With arterenol, t_1 is the time of the maximal arterial pressure response, and t_2 is the time of the minimal cerebrospinal fluid pressure response. With hyperventilation, t_1 is the time of the minimal pressure responses. The symbols indicating pressure are as in Figure 2. The dose of arterenol is given intravenously in micrograms (γ).

1 and 2). In contrast, arterenol and hyperventilation both decrease the fluid pressure after half a minute, while arterenol increases and hyperventilation decreases the arterial pressure (Fig. 2; Tables 2 and 3).

COMMENT

The peak responses of the cerebrospinal fluid and arterial pressures do not correspond after the administration of amyl nitrite and arterenol. The cerebrospinal fluid pressure rises immediately with amyl nitrite, but the peak rise occurs some time after the maximum drop in arterial pressure (Fig. 1). It is as though the cerebral flow initially increases, owing to cerebral arteriolar dilation, even though the inflow pressure has dropped; with recovery of the head of pressure, the flow increases further because the vessels are still dilated. The immediate effect of arterenol is a rise in cerebrospinal fluid pressure; the fall appears later (Fig. 2), an action which may be explained if it is assumed that the inflow pressure head has risen before the cerebral arterioles constrict. When the constriction appears, the flow drops despite the increased head of pressure, suggesting that arterenol increases the cardiac output, and therefore the cerebral flow, by a direct effect on the myocardium before peripheral vasoconstriction begins. Thus, it is unnecessary to make the less likely assumption that the cerebral vasoconstriction appears later than the generalized vasoconstriction. Arterenol does not increase the cardiac output when it is given by infusion at a constant rate of about 10 γ per minute.[7] The acute effect on the cardiac output of 10 γ doses given rapidly has not been studied to our knowledge; so we know of no experimental evidence which contradicts this explanation.

The data establish without question that changes in the arterial cerebrospinal fluid and jugular venous pressures may be completely dissociated. There are certain limitations to the inferences that may be drawn as a result of this proved dissociation. The acute effects of amyl nitrite and arterenol on the cerebral flow have not been measured directly because the present techniques for quantitatively measuring flow are not valid for studying such transient changes; and we know of no definitive evidence from the work of others that amyl nitrite, like carbon dioxide, increases cerebral flow, or that arterenol, like hyperventilation, decreases cerebral flow. Because the assumption is reasonable that they have these effects on cerebral flow, and because there is no simple alternative assumption that explains the observed concomitant changes in the several pressures, the observations support the hypothesis that changes in cerebral flow always induce changes in cerebrospinal fluid pressure in the same direction.

CONCLUSIONS

1. Changes in cerebral blood flow induce changes in cerebrospinal fluid pressure in the same direction.

2. Changes in cerebral blood flow and in the arterial and jugular venous pressures may be completely dissociated.

3. The magnitude of a change in cerebrospinal fluid pressure due to a given change in flow is increased when the original cerebrospinal fluid pressure is elevated.

4. When the cerebrospinal fluid pressure varies concomitantly with changes in systemic arterial pressure, it is because the cerebral blood flow varies concomitantly with the changes in systemic arterial pressure.

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MODIFICATION OF EFFECT OF CEREBRAL BLOOD FLOW ON CEREBROSPINAL FLUID PRESSURE BY VARIATIONS IN CRANIOSPINAL BLOOD VOLUME

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CHANGES in cerebral blood flow induce changes in the cerebrospinal fluid pressure in the same direction.[1] This report presents evidence that changes in craniospinal blood volume modify the extent of this effect.

MATERIALS AND METHODS

The types of patients studied and the methods of continuously recording the several pressures of interest have been described.[2] The patients included in this report were all those who had pressure-volume curves determined[3] and had satisfactory recordings of the arterial pressures.

OBSERVATIONS

We have shown from the drug responses that variations in cerebrospinal fluid pressure associated with variations in arterial pressure are due not to changes in

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arterial or systemic venous pressure but to concomitant changes in cerebral blood flow.[1] The fluid pulses associated with systole and diastole, the "arterial" pulses, are due, therefore, to pulsatile changes in flow rather than to the measured variations in arterial pressure. It has been shown that changing the cerebrospinal fluid pressure by withdrawing fluid from and adding fluid to the cerebrospinal fluid space modifies the craniospinal blood volume[2]; therefore, we are testing the hypothesis that a change in craniospinal blood volume modifies the effect of the cerebral blood flow on the cerebrospinal fluid pressure by determining whether the magnitude of the "arterial" pulse of the cerebrospinal fluid depends on the fluid pressure. Others have observed that the "arterial" pulse is large when the fluid pressure is high; we are concerned with the cause of this augmentation. The accompanying figure illustrates the increase of the cerebrospinal fluid "arterial" pulse that results from increasing the fluid pressure by adding fluid to the lumbar subarachnoid-fluid space. The effect is the same when the fluid is added to the ventricles.

We may confine the first part of our analysis to a study of the increase in the "arterial" pulse pressure as the cerebrospinal fluid pressure is increased above its initial value. It may be seen by inspection of the accompanying table that there are several causes of variation in the recorded "arterial" pulses: (1) The pulses increase as the fluid pressure rises; (2) pulses at a given fluid pressure differ with the subject and (3) the responses of the pulses to an increase in fluid pressure differ with the subject. For each person the variation in the "arterial" pulse with the fluid pressure is well represented by the formula

$$Y = kx$$

when Y, is the expected "arterial" pulse pressure; k, a constant characteristic of each person, and x, the cerebrospinal fluid pressure referred to the point of inflection of the pressure-volume curve.

The fluid pressure is so referred as an empirical transformation, which eliminates another constant in the equation. How well this formula fits the observations may be judged by comparing $\Sigma(y - Y)^2$, the sum of the squares of the deviation of the observed "arterial" pulses from those calculated by the formula, with the total variance $\Sigma(y - \bar{y})^2$, which is the corresponding sum of the squares of the deviations from the mean, $\bar{y}$.[4] The formula accounts for 99.33% of the variance of y.

When the variance due to the individual differences in slopes is eliminated by taking a combined slope, m_A, for the 16 men, we find that

$$m_A = 0.179 \pm 0.013,\ t = 13.3,\ P << 0.001$$

and the formula then accounts for 85.1% of the observed variation in pulse pressures. These two comparisons are a measure of the relative importance of individual and group responses in "arterial" pulses to the experimental situation.

We may test the hypothesis that there is no further drop in the "arterial" pulses as this fluid pressure is lowered below the initial pressure by testing the significance of the mean of the individual differences in pulse pressure, $\bar{\Delta}_A$, at the initial and minimal cerebro-spinal fluid pressures:

$$\bar{\Delta}_A = 14.6 \pm 3.6;\ t = 4.07;\ P = 0.001$$

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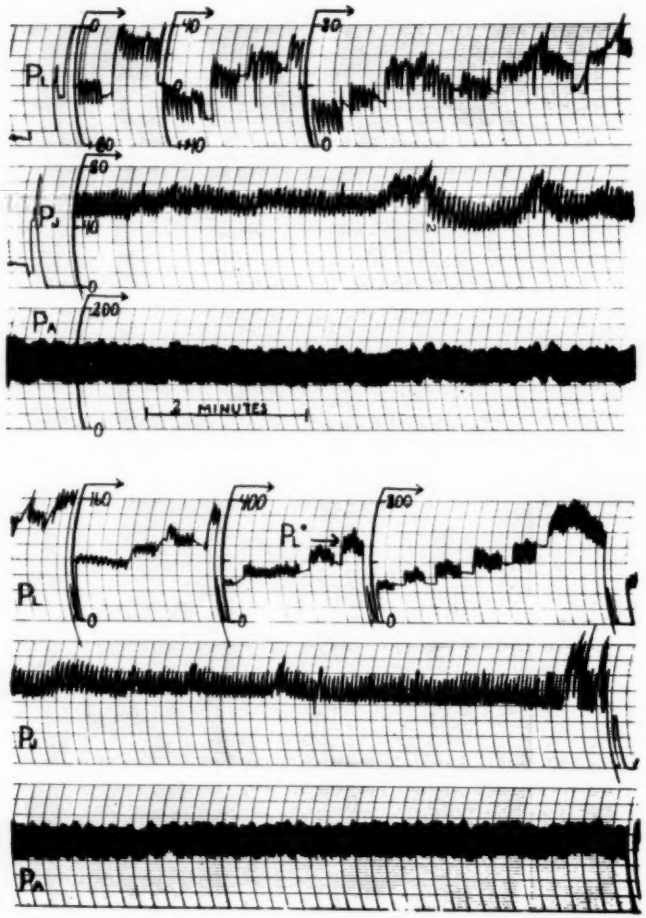

The tracings are from the record of woman aged 45 taken two weeks before operation for a metastatic lesion of the skull. The lumbar subarachnoid fluid pressure P_L, and the internal jugular venous pressure, P_J, are expressed in millimeters of water. In the initial portion of the top line, P_L is negative with respect to the atrial level. The brachial arterial pressure, P_A, is recorded in millimeters of mercury. The changes in P_L were induced by adding fluid to the lumbar subarachnoid fluid space in 2.5 ml. increments until the pressure reaches its initial value, P_L^*, and then in 2-ml. increments. When the fluid was added, the lumbar pressure was not being recorded. The attenuation of the amplifier recording P_L was changed in steps; at the end of the tracing the amplification was one-tenth that at the beginning.

*Relation of Cerebrospinal Fluid and Arterial Mean Pressures to Pulse Pressures at Various Cerebrospinal Fluid Pressures**

Patient; Sex; Age; Diagnosis		Initial Pressure			Minimal Pressure			Maximal Pressure			Jugular Venous Pressure	"Outlet" Pressure
		Mean	Arterial	Respiratory	Mean	Arterial	Respiratory	Mean	Arterial	Respiratory		
Alex; M; 60; herniated intervertebral disk	Pf	200	42	20	160	8	28	1,100	200	30	80	100
	Pa	128	70	6	110	60	7	117	65	7	..	..
Beau; M; 47; cerebral thrombosis	Pf	95	4	8	40	4	8	770	100	25	60	60
	Pa	90	45	4	93	40	3	110	60	5	..	..
Bowe; M; 69; cerebral contusion	Pf	200	25	20	60	12	6	1,200	150	75	..	80
	Pa	90	105	7	90	105	18	125	105	24	..	..
Call; M; 70; cerebral contusion	Pf	160	20	8	—50	14	10	765	140	40	80	85
	Pa	109	72	4	98	55	5	103	55	4	..	..
Clea; M; 36; chronic subdural hematoma	Pf	210	25	6	10	4	2	725	100	20	120	60
	Pa	90	60	3	83	40	4	68	40	3	..	..
Clem; M; 50; cerebral contusion	Pf	105	2	8	—160	8	28	500	60	20	75	75
	Pa	82	37	5	87	35	5	95	45	5	..	..
Felt; M; 64; cerebral contusion	Pf	135	12	40	—50	1	16	1,000	140	40	120	30
	Pa	97	50	6	87	50	2	100	55	4	..	..
Fiel; M; 40; posttraumatic epilepsy	Pf	160	30	8	55	10	10	650	250	50	130	25
	Pa	87	50	6	90	45	5	86	47	4	..	..
Floy; M; 47; cerebral contusion	Pf	175	12	4	90	1	5	820	140	20	150	110
	Pa	93	40	2	92	35	5	98	40	3	..	..
Gull; M; 31; posttraumatic cyst	Pf	80	8	3	—200	4	4	510	40	10	50	30
	Pa	87	42	2	98	38	3	82	37	2	..	..
Hass; M; 49; cerebral contusion	Pf	420	32	8	25	1	4	1,250	200	40	80	50
	Pa	98	40	1	112	42	1	123	70	5	..	..
Jane; F; 45; metastatic neoplasm to skull	Pf	310	40	10	—45	4	16	700	140	40	55	35
	Pa	99	62	2	97	65	5	109	49	3	..	..
Mont; M; 27; chronic subdural hematoma	Pf	140	2	12	—80	2	24	600	70	20	80	60
	Pa	108	40	4	107	42	10	95	30	5	..	..
Moor; F; 45; cerebral contusion	Pf	220	20	20	—170	10	10	940	160	50	80	40
	Pa	85	45	2	90	55	7	92	72	5	..	..
Neel; M; 26; chronic subdural hematoma	Pf	190	2	20	35	1	6	800	80	80	100	115
	Pa	86	43	5	90	52	10	93	50	15	..	..
Whit; M; 55; brain tumor, metastatic	Pf	400	40	40	125	1	15	850	250	50	400	300
	Pa	108	70	4	117	65	5	115	65	6	..	..

* The fluid pressures are expressed in millimeters of water, and the arterial pressures, in millimeters of mercury. "Initial," "minimal," and "maximal" refer to the pressures at the start of the procedure, at the time when the fluid pressure was least and at the time when it was highest. The "mean" refers to the arithmetical mean pressure over a respiratory cycle for the fluid pressure, and the diastolic pressure plus one-third the difference between the systolic and the diastolic pressure over a respiratory cycle for the arterial pressure. "Arterial" refers to the maximal deviation in pressure during systole and diastole, and "respiratory," to the difference between the mean systolic and diastolic pressures during quiet breathing. The jugular venous pressure, in millimeters of water, was that at the start of the procedure. The "outlet" pressure is the parameter, *b*, of the pressure-volume curve [3] and is expressed in millimeters of water. All the pressures were referred to the atrial level. The sex, age in years, and diagnosis are indicated under the patient's code letters.

It is most unlikely that the further drop in "arterial" pulse pressure was not real.

COMMENT

The hypothesis that the magnitude of the "arterial" pulses depends on the craniospinal blood volume has been established. Persons differ in that they have different pulse pressures at a given fluid pressure, referred to the point of inflection of the pressure-volume curve. The linear rates of change of the "arterial" pulses with the referred fluid pressure are different as the latter approaches its point of reference. These individual differences are relatively unimportant; most of the variation is accounted for by the mean change in craniospinal blood volume. The linear relationship fails as the fluid pressure approaches the point of inflection of the pressure-volume curve, but the "arterial" pulses continue to diminish as the pressure continues downward.

CONCLUSIONS

1. The effect of the cerebral blood flow on the cerebrospinal fluid pressure is modified by changes in the craniospinal blood volume.

2. This effect is the principal determinant of the magnitude of the cerebrospinal fluid "arterial" pulse when the fluid pressure is high.

3. The effect of a change in cerebral blood flow on the cerebrospinal fluid pressure is great when the fluid pressure is elevated, diminishes progressively with the fluid pressure, and becomes unimportant when the fluid pressure is below normal.

EFFECT OF CHANGES IN SYSTEMIC VENOUS PRESSURE ON CEREBROSPINAL FLUID PRESSURE

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THE RELATION between the cerebrospinal fluid pressure and the pressure in the internal jugular veins and in the intracranial venous sinuses has been studied by Becht,[1] Weed and Flexner,[2] and Bedford.[3] In substance, they found that the venous pressure was not modified essentially by changes in cerebrospinal fluid pressure, but that the fluid pressure was modified to some extent by changes in the venous pressure. None of them reported the effects of concomitant changes in both variables. We are presenting such observations because of their theoretical importance in a study of the factors controlling the cerebrospinal fluid pressure.

MATERIALS AND METHODS

The types of patients studied and the methods of continuously recording the several pressures of interest have been described.[4]

OBSERVATIONS

The Valsalva procedure shows how dependent the cerebrospinal fluid pressure is on the systemic venous pressure. When the Valsalva experiment is performed at

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3. Bedford, T. H. B.: Effect of Increased Intracranial Venous Pressure on the Pressure of the Cerebrospinal Fluid, Brain **58**:427-447, 1935.

4. Ryder, H. W.; Espey, F. F.; Kimbell, F. D.; Penka, E. J.; Rosenauer, A.; Podolsky, B., and Evans, J. P.: Mechanism of the Change in Cerebrospinal Fluid Pressure Following an Induced Change in the Volume of the Fluid Space, unpublished study.

initial fluid pressures and on pressures which are varied by adding fluid to or withdrawing fluid from the cerebrospinal fluid space, it has the same effect on the internal jugular venous and arterial pressures at these various fluid pressures, but the effect on the fluid pressure is contingent on its initial value (Fig. 1). During the time that the intrathoracic pressure is high, the fluid pressure is modified. The difference between the fluid pressure and the jugular venous pressure is a function of the initial fluid pressure (Fig. 2; Table). With the release of the high intrathoracic pressure, there is a surge in fluid pressure, as Hamilton, Woodbury, and Harper observed.[5] The height of the surge depends on the initial fluid pressure (Table).

The variations in cerebrospinal fluid pressure associated with quiet breathing may also be studied as the cerebrospinal fluid pressure is modified by changing the

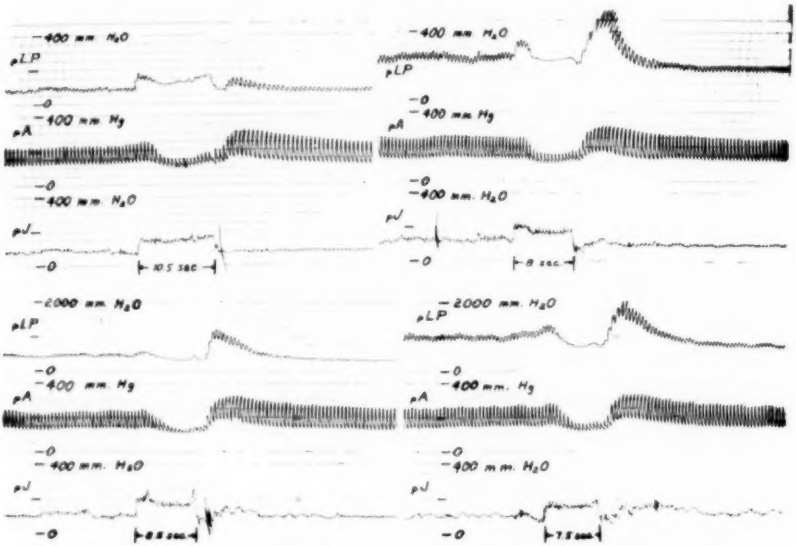

Fig. 1.—The four sets of tracings are 50-second sections from the continuous tracings of the lumbar subarachnoid fluid pressure, p^{LP}, the brachial arterial pressure, p^{A}, and the internal jugular venous pressure, p^{J}, of a woman of 60 who had had a hemorrhage from the right middle cerebral artery one week before the study. The initial lumbar pressure was 150 mm. of water. It was modified between the sets by the withdrawal or addition of water from or to the lumbar subarachnoid fluid space. During the time the jugular venous pressure was elevated, a pressure mask was held tightly over the mouth and nose at an internal pressure of 25 mm. of mercury.

volume of the cerebrospinal fluid space. If the effects of the systemic venous pressure on the fluid pressure are additive, then the cerebrospinal fluid "respiratory" pulsations will not increase as the fluid pressure increases with the changes in the craniospinal blood volume.[4] Regularity of the "respiratory" pulsations would contrast sharply with the increase in the "arterial" pulsations. The figure in a previous paper shows that the slow "respiratory" oscillations in fluid pressure are

5. Hamilton, W. F.; Woodbury, R. A., and Harper, H. T., Jr.: Physiologic Relationships Between Intrathoracic, Intraspinal and Arterial Pressures, J. A. M. A. **107**:853-856, 1936.

prominent at low pressures, and the fast "arterial" oscillations are so striking at high pressures that they obscure the "respiratory" pulses.

The hypothesis that the "respiratory" pulse pressure does not increase with an increase in cerebrospinal fluid pressure above its initial value may be tested by the following formula

$$Z = k'x^3$$

where Z is the expected "respiratory" pulse pressure; k', a constant characteristic of each person, and x, the cerebrospinal fluid pressure referred to the point of inflection of the pressure-volume curve.

From the data in the table previously presented,[6] it may be calculated that the formula accounts for 90.9% of the variance in the "respiratory" pulses as the cerebrospinal fluid pressure increases above its initial value. Using an estimate of the slope, m_R, obtained from all the men, we find

$$m_R = 0.051 \pm 0.005; \quad t = 10.0; \quad P << 0.001$$

and the formula still accounts for 76.3% of the total variation in the "respiratory" pulses as the cerebrospinal fluid pressure increases. The hypothesis that the

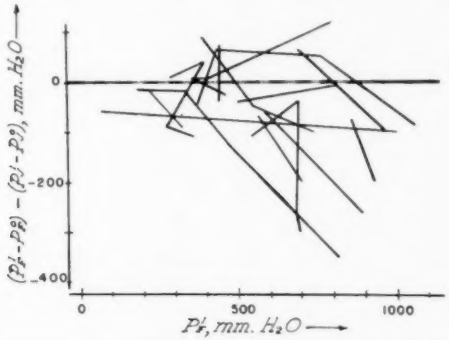

Fig. 2.—Relation between the difference in relative cerebrospinal fluid pressures ($P_V{}^1 - P_V{}^0$) and relative internal jugular venous pressures ($P_J{}^1 - P_J{}^0$) and the fluid pressure ($P_V{}^1$). The superscripts refer to the time when the intrathoracic pressure was elevated by performance of the Valsalva procedure (time t_1) and before its performance (time t_0).

"respiratory" pulse pressure does not increase as the cerebrospinal fluid pressure increases above its initial value is false.

We may test the hypothesis that there is no difference in the relative effect of the increase in fluid pressure on the "arterial" and "respiratory" pulses by determining the significance of the difference in mean slopes,

$$m_A - m_R = (0.179 - 0.051) \pm 0.014 = 0.128 \pm 0.014; \quad t = 9.14; \quad P << 0.001$$

or by testing the mean difference in the individual slopes

$$\Delta_{A-R} = 0.137 \pm 0.029; \quad t = 4.64; \quad P < 0.001$$

This hypothesis is also highly improbable. There is an important difference in the responses. Increasing the cerebrospinal fluid pressure above its initial value has

6. Ryder, H. W.; Espey, F. F.; Kimbell, F. D.; Penka, E. J.; Rosenauer, A.; Podolsky, B., and Evans, J. P.: Modification of Effect of Cerebral Blood Flow on Cerebrospinal Fluid Pressure by Variations in Craniospinal Blood Volume, A. M. A. Arch. Neurol. & Psychiat., this issue.

three and a half times as great an effect on the "arterial" pulses as it has on the "respiratory" pulses.

We may also test the hypothesis that lowering the cerebrospinal fluid pressure below its initial value does not reduce the amplitude of the "respiratory" pulses. We find

$$\bar{\Delta}_R = 2.7 \pm 3.1;\ t = 0.88;\ P \sim 0.4$$

*Effect of Valsalva Procedure on Cerebrospinal Fluid and Jugular Venous Pressures, at Different Cerebrospinal Fluid Pressures**

Patient; Sex; Age	t_0		t_1		t_2		t_3		Surge $(P_F - P_J)_3 - (P_F - P_J)_2$
	P_F	P_J	P_F	P_J	P_F	P_J	P_F	P_J	
Ande; M; 74	60†	50	350	380	85	75	105	70	25
	130	40	440	290	280	50	370	45	95
	450	40	750	290	500	60	580	30	110
	775	25	1,050	385	700	50	975	80	245
Brow; M; 18	250†	25	560	400	350	160	400	100	110
	525	25	700	400	530	150	1,050	110	560
Call; M; 70	10†	90	500	620	40	50	70	100	−20
	340	40	800	510	300	90	840	75	555
Clea; M; 36	210†	110	600	530	200	80	380	120	140
	700	60	960	400	680	80	1,140	80	460
Davi; M; 56	20	75	70	180	25	80	35	100	−10
	140†	80	340	350	160	130	275	195	50
	1,000	90	1,000	190	950	85	1,100	100	135
Felt; M; 64	−30	80	540	760	0	100	20	130	−10
	180†	110	680	660	140	80	550	120	370
	540	100	680	500	280	100	720	70	470
	700	20	700	330	420	110	960	80	570
Flrt; M; 46	175†	70	575	500	210	100	480	125	245
	700	50	890	500	510†	100	850	75	365
Harr; M; 27	200†	125	850	850	200	115	435	135	215
	400	100	925	825	350	100	800	110	440
Henr; M; 61	−50	20	275	340	0	50	5	45	10
	50†	40	400	350	90	40	180	35	95
	160	25	270	230	165	40	260	50	85
	215	15	360	270	200	10	365	40	135
Holz; M; 22	110†	150	360	400	255	190	175	220	−110
	190	170	390	370	210	180	240	200	10
	450	180	800	410	525	210	725	270	140
Jame; F; 45	−80	50	380	420	−20	70	0	90	0
	250†	60	550	410	240	60	300	70	50
	480	40	740	400	460	60	540	70	70
Kayt; F; 60	85†	70	170	170	70	65	120	80	35
	180	35	335	210	250	90	270	115	−5
	440	105	460	250	325	60	1,060	120	675
	1,050	70	825	190	675	80	810	165	50
Lamb; M; 32	155†	105	460	260	225	115	325	160	55
	510	90	800	250	600	100	925	130	295
Lemo; M; 67	125†	100	435	340	130	85	160	130	−15
	250	30	440	280	250	70	260	70	10
Pier; F; 82	60†	0	350	285	130	10	130	40	−30
	160	15	460	345	150	0	380	20	210
Slau; M; 56	50	10	215	190	60	30	90	55	5
	80†	10	245	210	95	40	135	75	5
	170	20	325	270	120	25	330	100	135
Stal; M; 79	60†	70	670	305	100	130	260	200	90
	300	120	940	340	170	150	650	140	490
Wils; M; 55	50†	125	540	375	100	125	140	180	−15
	275	160	1,000	200	375	140	950	175	540
	1,000	125	1,100	200	750	125	1,650	150	875

* The data recorded are those of all patients who performed the Valsalva procedure at different cerebrospinal fluid pressures at the start of the procedure, with certain qualifications. The duration of the breath holding and the intensity of the effort (as measured by the venous and arterial pressure responses) were comparable; the pressures were free of artifact; essentially duplicate responses were omitted. The cerebrospinal fluid pressures (P_F) were varied by the withdrawal of fluid from or the addition of fluid to the subarachnoid space. The conditions nearest the patient's equilibrium pressure are indicated by the dagger. P_J indicates the internal jugular pressure; t_0 refers to the time at the start of the procedure; t_1, the time just before the high intrathoracic pressure was released; t_2, the time when the arterial pressure was minimal, and t_3, the time when the arterial pressure, or the surge in intracranial pressure, was maximal.

The hypothesis is correct. At cerebrospinal fluid pressures normal and below normal, the "respiratory" pulses are not influenced by the change in fluid pressure.

COMMENT

During and following the Valsalva procedure the cerebrospinal fluid pressure usually varies concomitantly with the changes in arterial and systemic venous pressure, but it is not passively dependent upon changes in either the arterial or the systemic venous pressure because the initial fluid pressure modifies only the fluid-pressure response. Frequently the fluid pressure drops during the time the intrathoracic pressure is elevated and the initial fluid pressure is high. The fluid pressure following the procedure varies from an imperceptible rise to a surge of nearly 1,000 mm. of water, depending on the initial pressure. We may explain these variations if we assume that the cerebral blood flow in this case varies with the systemic arterial pressure. The effect of the cerebral blood flow on the cerebrospinal fluid pressure [7] is increased when the fluid pressure is high.[6] The effect of the Valsalva procedure on the fluid pressure is the resultant of the effects of blood flow and systemic venous pressure.

The respiratory variations in the cerebrospinal fluid pressure are increased when the fluid pressure is high, just as the arterial variations are.[6] In seeking an explanation for this effect, we may consider that the increase in the "arterial" pulses is three and a half times as great as that of the "respiratory" pulses, that the arterial pulses continue to fall as the fluid pressure is lowered to negative values, while the "respiratory" pulses do not, and that there are variations in the systemic arterial pressure with respirations. We may assume that the respiratory variations in the mean arterial pressure cause minor changes in the rate of cerebral blood flow, just as we assumed that the Valsalva procedure induced major changes in flow. These concomitant changes in flow increase the "respiratory" pulses at high fluid pressures, but this increase is minor.

While these considerations are not quantitative, the simplest assumption that we can make to explain the observations is that the effect of the cerebral blood flow accounts entirely for the variations in the response of the fluid pressure at high pressures to minor, as well as to major, fluctuations in the systemic venous pressure. At fluid pressures which are normal and below normal, the "respiratory" pulses are not modified by changing the fluid pressure, and the surges following the Valsalva procedure are relatively insignificant. The effect of the cerebral blood flow on the fluid pressure is slight at low pressures. This strengthens the assumption that the systemic venous pressure acts simply as a reference level for the craniospinal fluid and vascular pressures at any level of any of the pressures.

CONCLUSIONS

1. Isolated changes in the systemic venous pressure cause additive changes in the cerebrospinal fluid pressure.

2. Changes in the systemic venous pressure are rarely isolated from changes in the rate of cerebral blood flow, so that the response of the cerebrospinal fluid to a change in systemic venous pressure is usually modified by the effects of concomitant changes in cerebral blood flow.

3. The systemic venous pressure may be considered a reference level for the craniospinal fluid and vascular pressures, at any level of any of the pressures.

7. Ryder, H. W.; Espey, F. F.; Kimbell, F. D.; Penka, E. J.; Rosenauer, A.; Podolsky, B., and Evans, J. P.: Influence of Changes in Cerebral Blood Flow on the Cerebrospinal Fluid Pressure, A. M. A. Arch. Neurol. & Psychiat., this issue, p. 165.

MANAGEMENT OF ACUTE EPISODES IN MULTIPLE SCLEROSIS

A Preliminary Report

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NEW YORK

THE PROBLEM

STUDIES made several years ago by Brickner and Franklin [1] and Franklin and Brickner [2] showed that some of the symptoms of multiple sclerosis could be reduced or abolished promptly with vasodilating drugs. Constrictions seen in retinal arterioles often appeared to be associated with scotomas; both constrictions and scotomas were affected by the drugs. From these and certain related observations the theory was evolved that at least some of the lesions are the consequence of vasospasm,[3] with or without associated thrombosis (Putnam and others [4]). Photographs of constrictions will appear in another communication.[5]

Franklin and I were unable at that time to apply these findings in such a way as to make them of definite therapeutic use. Others have since made efforts to do so. Previous efforts had been made to use vasodilation therapeutically, for other reasons. However, even though some of the results have been encouraging, the authors have not been satisfied that the problem of spontaneous remissions was fully controlled.

Recently I have renewed vasodilation studies. My aim has been to learn whether the employment of certain standards of evaluation might not make the problem of spontaneous remissions less difficult to deal with and show more definitely whether vasodilating drugs (or any other rapidly acting drug it is desired to test) can be effectively used in the treatment of new symptoms. Examination of the new observations and restudy of some of the old ones in the light of these standards

These studies were supported by the Fund for Reasearch, Inc., and the National Multiple Sclerosis Society.

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Service, Mount Sinai Hospital, New York, Drs. I. S. Wechsler and M. Bender, successive Chiefs.

1. Brickner, R. M., and Franklin, C. R.: Visible Retinal Arteriolar Spasm Associated with Multiple Sclerosis, Arch. Neurol. & Psychiat. **51**:573, 1944.

2. Franklin, C. R., and Brickner, R. M.: Vasospasm Associated with Multiple Sclerosis, Arch. Neurol. & Psychiat. **58**:125, 1947.

3. (*a*) Brickner and Franklin.[1] (*b*) Franklin and Brickner.[2] (*c*) Brickner, R. M.: Significance of Localized Vasoconstrictions in Multiple Sclerosis, A. Res. Nerv. & Ment. Dis. Proc. **28**:236, 1950.

4. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298, 1937. Putnam, T. J., and Adler, A.: Vascular Architecture of the Lesions of Multiple Sclerosis, ibid. **38**:1, 1937. Fog, T.: Topographic Distribution of Plaques in Spinal Cord in Multiple Sclerosis, ibid. **63**:382, 1950.

5. Franklin, C. R., and Brickner, R. M.: To be published.

suggest the possibility of affirmative answers to both questions, if sufficiently detailed care is employed in the studies.

The first two of these standards have been described before, but not together, nor were they used in the manner employed in this communication. The third is new. The aggregate of the three standards appears to offer a new total approach to the evaluation of treatment by rapidly acting drugs.

The standards and their employment depend upon the reversibility of some of the symptomatic phenomena of multiple sclerosis.

Reversibility of Many New Symptoms.[3a-c]—Most of the symptoms originally reported as affected by the drugs were known to be new ones, and it was assumed that the others which could be so influenced were also new, or relatively so, as compared with the symptoms which were not influenced. Other investigators who have confirmed these observations have also noted that it was the relatively new phenomena which seemed mainly to be affected. The evidence from all these observations suggests that many phenomena of multiple sclerosis are reversible for a while but later become irreversible. According to the theory already proposed, irreversibility occurs when tissue death has ensued from too prolonged or too complete vasospasm, sometimes accompanied by thrombosis.

STANDARDS OF EVALUATION OF THERAPY

The standards may be summarized as follows:

1. *Reversible Symptoms Used as Yardsticks.*—In almost all therapeutic studies, investigators have concentrated on the total course of the disease while the patient was receiving whatever medication was being tested. This also has been the foundation of most of the therapeutic work with vasodilation, with certain exceptions, to be discussed later.

However, when rapidly acting drugs are being tested, attention should be centered, not on the long-term course of the disease, but on the immediate fate of the symptoms which prove to be reversible. The reversible phenomena can then be used as yardsticks by which the effectiveness of the drug may be measured. If a given drug or mode of treatment can be shown to affect all or some of the reversible phenomena favorably, predictably, and repeatedly, it would seem correct to regard it as therapeutically effective.

2. *Immediacy of Effect as the Critical Factor in Evaluation.*—The critical points in evaluation are as follows: The drug must be a rapidly acting one, such as a fast-acting vasodilator, and the phenomenon being used as a yardstick must be affected within a few minutes of the start of action of the drug. With vasodilating drugs specifically, if the degree of the phenomenon is regularly diminished within a few minutes of the onset of the flush in a sufficient number of observations the possibility becomes great that the effect is due to the action of the drug, and not to a spontaneous remission.

3. *Predictable Repetition of Effect.*—Sometimes relief of a phenomenon serving as a yardstick is long-lasting, but sometimes the symptom returns in a few hours. When it returns, vasodilation should again reduce or abolish it. It should be possible to repeat this effect predictably without limit unless tissue death occurs between administrations of the drug.

Employment of these standards should make it possible to avoid the long periods of observation previously deemed necessary for evaluation of treatment.[6]

REPORTS OF OTHER INVESTIGATORS

Vasodilation Studies.—Although the studies of others have not been therapeutically conclusive, some have been confirmatory of the original observations concerning the prompt effect of vasodilation on new symptoms. From the standpoint of confirmation, these studies may be divided into three groups: In Group A, effects on symptoms were evaluated within a matter of minutes of administration of the drug. Positive results obtained by this mode of assay are regarded as giving close confirmation. In Group B are included a few additional observations in which about an hour elapsed before a change was looked for and found; these results are regarded as giving fair confirmation. Only one such observation is included in this communication (personal observation, not from the literature). (The status of a group is given in these observations so that I may have a way of referring to them.) In Group C effects were evaluated only after one to several days of treatment. This method of assay is not precise, and it does not control the problem of spontaneous remission, although it may be said to move in that direction if the number of cases apparently favorably influenced is large enough. Group C is regarded as tending toward confirmation.

Group C: The fact that this group has always been the largest explains why the observers had deemed the question of spontaneous remissions not fully dealt with. This group will be considered first.

Bell, Williams, and Karnosh[7] employed tetraethylammonium chloride in 14 cases, and Williams, Karnosh, and Tucker[8] used it in a larger group, which included 79 "acute" cases, in which symptoms were of two months' duration or less or in which an acute exacerbation occurred on a chronic background. Of these 79 cases, "good subjective and some objective" improvement occurred in 12, and "fairly good subjective and minimal objective improvement" resulted in 24; in 22 cases there was "fair subjective and no objective improvement." In both series, results were evaluated after a few days, rather than minutes, of treatment. In another communication, Williams and Bell[9] said: "A majority of the patients with an acute relapse apparently begin definite improvement within three to five days after the start of treatment." These authors added that relapses were neither completely cleared nor entirely prevented by tetraethylammonium chloride, though it was their belief that the drug "produces a definite and beneficial effect on most cases."

6. Simon, B., and Solomon, P.: Multiple Sclerosis: Effect of Typhoid Vaccine and of Epinephrine on Coagulation of Blood, Arch. Neurol. & Psychiat. **34**:1286, 1935. Simon, B.: Blood Coagulation in Multiple Sclerosis and Other Diseases of Brain and Spinal Cord, ibid. **34**:1296, 1935. Nathanson, M., and Savitsky, P.: Platelet Adhesive Index Studies in Multiple Sclerosis and Other Neurological Diseases, to be published. Roizin, L.; Abel, R., and Winn, J.: Preliminary Studies of Sludge Blood in Multiple Sclerosis, to be published.

7. Bell, E. Jr.; Williams, G. H., and Karnosh, L. J.: Tetraethylammonium Chloride in Multiple Sclerosis, Cleveland Clin. Quart. **15**:90, 1948.

8. Williams, G. H.; Karnosh, L. J., and Tucker, H. J.: Modification of Signs in Multiple Sclerosis Through the Use of Tetraethylammonium Chloride, Neurology, to be published.

9. Williams, G. H., and Bell, E., Jr.: Present Day Status of Multiple Sclerosis, Mississippi Doctor **27**:130, 1949.

Schmid [10] observed "unequivocal improvement in 26 of 28 cases within approximately a day of the use of vasodilatation therapy."

GROUP A: Bell [11] mentioned three cases in which effects were noted within one-half hour. Very rapid changes were not looked for in most cases.

Schmid [10] told of five instances in which he reexamined patients within a few minutes and found abrupt improvement.

Bente and Betz,[12] in their report on vegetative phenomena in multiple sclerosis, mentioned a patient whose regular morning aggravation of symptoms could be prevented by hydergine (dihydrogenated ergot alkaloids).

Presumably Related Evidence.—Cobb [13] has reported the helpfulness of carbon dioxide inhalations in treating patients with cerebral ischemia. In particular, elderly arteriosclerotic patients with transient periods of confusion, forgetfulness, and spells of partial aphasia were benefited. Treatment must be given within a few hours of the onset of symptoms.

Other Vasodilation Studies in Multiple Sclerosis.—All these studies belong in Group C. The first attempt to treat multiple sclerosis by vasodilation was made by Moore [14] in 1940, in an ingenious effort to obtain the possible benefits of fever treatment without its disadvantages. He was also stimulated by suggestions inherent in Putnam's [4] demonstration of thrombi in small vessels in and near lesions. Moore treated five patients with advanced disease, probably all of the chronic progressive form, and reported notable improvement in all of them. Periods of omission of treatment were associated with regression. Much of the improvement may have been an effect on spasticity (see below).

Royle [15] tested the effects of vasodilation produced by section of the thoracic sympathetic trunk and reported good results in four cases. He thought that the promptness of effect was strong evidence against spontaneous remissions. Previously Royle [16] had reported that surgical procedures on the sympathetic nervous system were followed by improvement in spasticity in various other types of neurological disturbance and by improvement in trigeminal neuralgia. Hence the specificity of application of his work to the problem of multiple sclerosis is uncertain.

Wetherell,[17] prompted by Royle's work and the investigations of Putnam,[4] also performed cervicothoracic sympathectomy and reported favorable results in one case. Koch and de Savitsch [18] also destroyed parts of the sympathetic nervous

10. Schmid, E. E.: Personal communication to the author.

11. Bell, E. Jr.: Personal communication to the author.

12. Bente, D., and Betz, K.: Über eigenartige vegetativ bedingte Phänomene bei der multiplen Sklerose, Arch. Psychiat. **185**:524, 1950.

13. Cobb, S.: Gefässerweiternde Therapie cerebraler Gefässerkrankung, Monatsschr. Psychiat. u. Neurol. **117**:213, 1949.

14. Moore, M. T.: Treatment of Multiple Sclerosis with Nicotinic Acid and Vitamin B_1, Arch. Int. Med. **65**:1, 1940.

15. Royle, N. D.: Surgical Treatment of Disseminated Sclerosis, M. J. Australia **1**:586, 1933.

16. Royle, N. D.: Observations on the Alteration of the Circulation of the Brain by Surgical Means in Diseases of the Central Nervous System, Brit. M. J. **1**:1063, 1932.

17. Wetherell, F.: Multiple Sclerosis: Cervicodorsal Sympathectomy as a Relief Measure: Report of a Case, J. A. M. A. **102**:1754, 1934.

18. Koch, C. F., and de Savitsch, E.: Surgical Treatment of Disseminated Sclerosis by Sympathectomy and Ganglionectomy: Technique by the Anterior Approach, Brit. M. J. **1**:1254, 1938.

system and reported improvement in 10 cases, all in the advanced stage. Their work was also stimulated by Putnam's observations and by the reports of other surgeons. Horton, Wagener, Aita and Woltman,[19] initiated the use of histamine diphosphate in treating multiple sclerosis in 1944; the detailed reasons for doing so were not given. The results obtained were as follows: Of 24 patients with acute disease, 18 became essentially well, and only 3 were unimproved. Of 78 patients with advanced or chronic disease, 36 showed 10 to 95% improvement, and 42 showed subjective, but no objective, improvement. One patient with the acute stage had 24 injections of typhoid vaccine, without relief, but the patient became normal after 13 injections of histamine diphosphate.

In a later report, Horton and Wagener[20] reported on the treatment with histamine diphosphate of 61 patients with retrobulbar neuritis. Twenty-four patients regained normal vision, and 10 had 50 to 75% visual recovery. Eighteen of the group had had treatment with typhoid vaccine without regaining normal vision.

It was assumed that the improvement resulted from vasodilation in the central nervous system.

Jonez[21] reported enthusiastically on the use of histamine diphosphate in 152 cases. The underlying theory was the counteraction of allergy, not vasodilation as such. However, Jonez' patients also received tubocurarine chloride, U. S. P., and the precautions taken to control the problem of spontaneous remissions were not clearly set forth.

Arkin, Sherman, and Weinberg[22] concluded that tetraethylammonium chloride "had no influence on the course of multiple sclerosis." Their standards, which differed from those of the other workers, were carefully thought out and were planned with the idea of avoiding the habitual traps. Arkin and his co-workers did not give attention to the newness of the phenomena; their plan was to assign grades to the courses of various types of phenomena, such as gait and cerebellar signs, and position sense. They counted the number of phenomena which improved and the number which regressed over a given period and evaluated the treatment according to these scores.

From the standpoint of this study, the standards of Arkin and his co-workers, despite their careful consideration, are not designed to catch the effect of drugs with rapid, transient action. In fact, they illustrate what I believe to be one of the pitfalls in the evaluation of vasodilation therapy—the uncontrolled intervals between treatments, when the effects of vasodilation may have worn off. The neurological effects of a single flush may long outlast the flush itself (see below), but unless the effective period is known and certain other precautions are heeded, there are periods, of varying length, in which the patient must be regarded as not under treatment. New symptoms and regressions appearing in such periods cannot be used as yardsticks of treatment. For the same reason, improvement occurring at

19. Horton, B. T.; Wagener, H. P.; Aita, J. A., and Woltman, H. W.: Treatment of Multiple Sclerosis by the Intravenous Administration of Histamine, J. A. M. A. **124**:800, 1944.

20. Horton, B. T., and Wagener, H. P.: Retrobulbar Neuritis: Treatment with Histamine, J. Lab. & Clin. Med. **33**:1611, 1948.

21. Jonez, H. D.: Multiple Sclerosis and Allergy Management with Histamine Therapy, Ann. Surg. **8**:44, 1950.

22. Arkin, H.; Sherman, I. S., and Weinberg, S. L.: Tetraethylammonium Chloride in the Treatment of Multiple Sclerosis, Arch. Neurol. & Psychiat. **64**:536, 1950.

such times may not be related to the effects of the drug; this is the reason that the therapeutic work listed under Group C is at most only suggestive. Periods of at least eight hours, and probably much longer (during the night), occurred between treatments in the series of Arkin and his co-workers, since they gave tetraethylammonium chloride three times a day routinely.

VASODILATION THERAPY IN RELATION TO THE STANDARDS DESCRIBED

The current report deals with 11 cases. Ten of them have not previously been reported; in 7 of these the disease was characterized by acute episodes, and in 2 by a chronic progressive course without acute episodes. Two are old cases [2] with previously unreported or unevaluated material.

All but the two patients with chronic progressive disease responded to the drugs in such a way as to confirm the previous studies (32 observations on nine patients). Reversibility of new, or relatively new, symptoms was demonstrated again. The three standards described above were met; the effectiveness of rapidly acting vasodilating drugs was shown by the diminution or disappearance of symptoms within a few minutes of the administration of the drug. The symptoms which returned later (21 observations on five patients) met the third standard by

Reversibility of New Symptoms with Use of Vasodilating Drugs

	Observations	Cases
Franklin and Brickner	93	16
Bell, Karnosh, and Williams	3	3
Schmid	5	5
Bente and Betz	1	1
Current	32	9
Totals	134	34

responding again, regularly. In the two cases of chronic progressive multiple sclerosis the results were doubtful, but not necessarily negative.

SIGNIFICANCE OF DURATION OF BENEFICIAL EFFECTS OF A SINGLE VASODILATION

Reversibility of relatively new symptoms in association with the use of vasodilating drugs has now been seen at least 134 times in 34 cases, only observations of Groups A and B being counted (Table). Exclusive of the current series, this reversibility has been observed at least 102 times in 25 cases (only 1 observation being allowed for in each case). Hence it may be thought of as being reasonably soundly grounded.[23]

23. This is true in the face of the potential failure of some new or relatively new symptoms to respond. Improvement in all symptoms should not be expected, for reasons to be described. No statistics are available concerning how many new symptoms were unrecognized among the observations of the other investigators. In the series reported by Franklin and me, all new symptoms of which we were aware responded; however, our attention may have been too closely focused on single phenomena which could be measured with reasonable objectivity, and some new symptoms may have escaped notice. It is possible, and even probable, that some new or relatively new symptoms unrecognized as such failed to respond. In neither the original nor the current series was there lack of response by any symptom known to be only a few hours old. Between the performance of the original investigation and the current series, two fairly new,

(Footnote continued on next page)

All but the two cases of chronic progressive disease in the current series seem to demonstrate clearly a new point which is critical in conducting therapy; in these cases the results were not negative, but doubtful. The validity of the new point depends entirely upon the validity of the basic observation of reversibility. If the reversibility is deemed reasonably well demonstrated, then the new point, although so far limited to only nine cases, is also valid, for it is only a small variant of the basic point. The new point concerns the duration of the beneficial effect of a single vasodilation.

Although in the original studies [24] single symptoms were occasionally studied over an extended period and it was found that the same symptom, when it recurred, could be affected repeatedly by the drug, no daily observations were made, nor was the new symptom ever examined several times on the same day; that is, no attempt was made to follow the course of a given symptom closely and in systematic detail over an extended period. Hence it is not known how long beyond the extent of the flush the effects of a single vasodilation endured. Schmid,[10] however, noted the duration, at least in some cases.

One of the purposes of the present study has been to learn something of the duration of the effect on the symptoms (not merely the duration of vasodilation). The effect on symptoms has now been found ordinarily to outlast the flush, often by considerable lengths of time. Reduction or abolition of the symptom has been found to last from a few minutes to several days. Most of the patients so far studied in this manner seem to have their own characteristic duration of effect.

Application to Therapy of Long Duration of Effects of Each Vasodilation.—My previous belief was that vasodilation could not actually help a patient unless it endured 24 hours a day for exceedingly long periods, if not a lifetime; this state would be very difficult to achieve, even with drugs having extremely long-lasting vasodilating effects. This belief depended on (*a*) the assumption, now shown usually to be wrong, that the beneficial effect of the vasodilation probably did not last beyond the rather brief period of the flush itself, and (*b*) the mistaken concept that vasodilation therapy, to be useful, must be so given as to act prophylactically, preventing the inception of new phenomena.[3b,c] Williams and Bell [9] also thought it would be necessary to achieve "a more or less permanent vasodilatation" for long-term effects.

This concept is now replaced by another: The long duration of symptomatic effect, previously unknown, seems to make the use of vasodilating drugs practical without the undertaking of anything as difficult as permanent vasodilation.

If most new symptoms can be favorably influenced by vasodilation and the effects last a reasonable length of time, this fact should be made the focal point of therapy, with emphasis on the following principles:

1. Therapeutic attention should be placed upon new symptoms only, and not upon the whole array of symptoms.

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and hitherto unreported, symptoms have failed to respond. One was a new diplopia in Case D (Franklin and Brickner [2]); tests with papaverine hydrochloride, amyl nitrite, and histamine diphosphate on the 16th, 17th, and 18th days, respectively, after the onset failed to show reduction in the diplopia. The second was unilateral blurring of vision, which failed to respond to amyl nitrite the fourth day after the onset but disappeared spontaneously on the sixth day. In the current series, a scotoma in one case failed to give a definite response one month after the onset.

24. (*a*) Brickner and Franklin.[1] (*b*) Franklin and Brickner.[2]

2. The duration of effect of a given vasodilation should be determined for each symptom, with each patient; and treatment should be timed to coincide with the needs thus indicated. Vasodilation persisting 24 hours a day will not ordinarily be necessary.

3. Judging by the responses of new symptoms so far, most of them can be reduced almost to the zero point and held there. In no case was the amount of residual incapacity very large. All symptoms but one have been at least 36 hours old.

Although the prevention of new symptoms altogether would, of course, be better, a long-term prophylactic program with vasodilating drugs would be almost impossibly difficult to maintain; however, if the degree of alleviation of new symptoms already achieved could be regularly expected, it would be very helpful to the patient, even if not perfect. When feasible, new phenomena should be treated promptly, within minutes, or even seconds, by a self-administered vasodilating drug. By so doing, the amount of residual abnormality might still further be reduced.

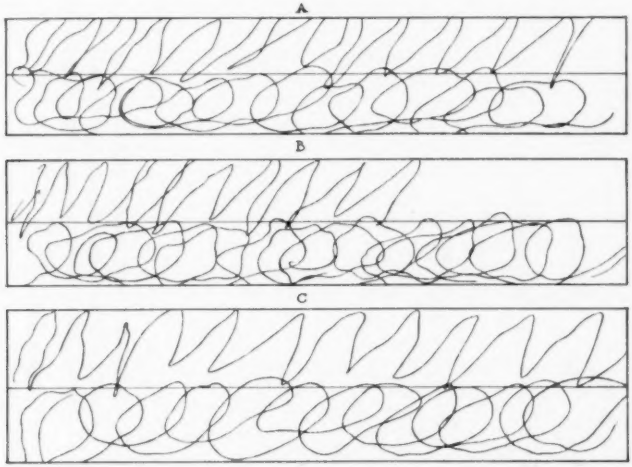

Fig. 1 (Case 1).—*A*, line drawing (4: 10 p. m.) with the left hand prior to medication. Medication (nicotinic acid, 100 mg. administered sublingually) was given at 4:20 p. m.

B and *C*, line drawings following medication, made at 4: 32 and 4: 34 p. m. The flush appeared between 4: 32 and 4: 34 p. m.

As has been stated, at present irreversibility is thought to depend upon tissue death from prolonged or very marked vasospasm, sometimes associated with thrombosis; the disturbances which are reversible are thought to result from mere hypoxia and malfunction without tissue death.[3b,c]

ACUTE EPISODES [25]

CASE 1.—N. K., a woman aged 28, had had multiple sclerosis for nine years. Her disease had been in remission about three years, with only minute residual visual symptoms.

25. Patients were referred by Drs. Bernard Glueck, Irville H. MacKinnon, Marvin Jones, Lydia Giberson, Albert J. Aptaker, and Robert B. Zatz, of New York; Dr. Robert Smith, of Booneville, N. Y., and Dr. Hugh F. Cook, Newark, N. J.

During the night of Jan. 22, 1952, she awoke with numbness and slight incoordination of the left hand and incoordination of the left lower extremity. Examination 36 hours later, on Jan. 24, showed moderate ataxia of both left extremities; the drawing of lines with the left hand was impaired (Fig. 1), and balance was disturbed in walking.

Jan. 24.—Nicotinic acid, 100 mg., was administered sublingually. Drawing of lines showed marked improvement during the flush (Fig. 1).

The duration of the flush was about 20 minutes; the duration of improvement, about 37 minutes. Thereafter, progressive regression of line drawing occurred.

Jan. 25.—Line drawing at 10 a. m. was a little better than on the last test, on Jan. 24 (attributed to overnight rest).

First Infusion of Histamine Diphosphate, from 10:50 to 10:55 a. m.: Ten cubic centimeters of a 0.5% solution was given by iontophoresis at 5 ma.[28] (Abramson[27]). There was no flush or change in line drawing.

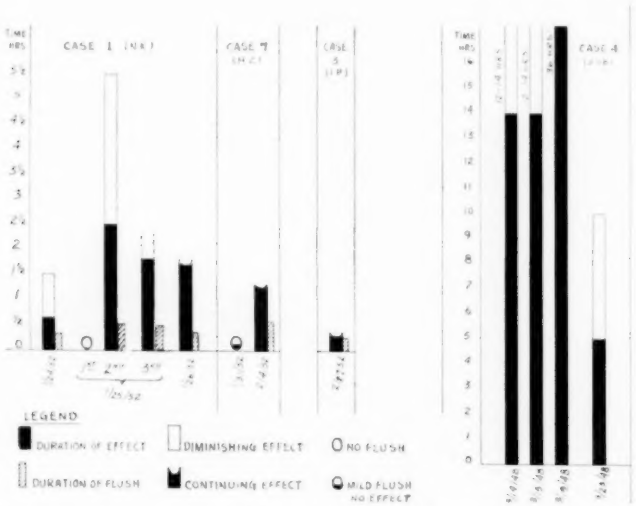

Fig. 2.—Duration of effects in Cases 1, 3, 4, and 7. The vertical broken lines in Case 1 signify that the duration of the beneficial effect persisted for a considerable, but unknown, length of time.

Second Infusion of Histamine Diphosphate, from 12:14 to 12:24 p.m.: Immediate improvement occurred with the beginning of the flush; this improvement was only moderate, for the line drawing was only moderately impaired beforehand.

The duration of the flush was about 34 minutes; the duration of improvement, about 2½ hours (Fig. 2).

One-Half Hour Later: The drawing of lines was worse than before induction of the first flush of the day. This effect may have been due to fatigue as time passed and effort was made (a habitual condition with this patient during periods of activity of the disease).

Third Histamine Infusion, from 4:08 to 4:18 p. m.: Immediate, pronounced improvement occurred with the beginning of the flush.

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26. These specifications were adhered to throughout with this patient.

27. Abramson, H. A.: Histamine Iontophoresis in the Therapy of Multiple Sclerosis, New York J. Med. **49**:1151, 1949.

The duration of the flush was about 30 minutes; 1½ hours later (5:30 p. m.), when the last test of the day was made, the improvement was still maintained at the same level (Fig. 2).

Jan. 26.—The first line drawing, at 7:30 a. m., was nearly normal. Slight regression occurred as the day passed, until, at 12:22 p. m., distinct dysfunction was visible.

Histamine Infusion from 12:34 to 12:44 p. m.: Distinct, immediate improvement occurred with the flush.

The duration of the flush was about 22 minutes; improvement continued through the time of writing, March 24, 1952 (Fig. 2).

After approximately a six-week interval, lines were drawn again to test the effect of lack of practice. The results were within normal limits, supporting the supposition that the improvement during the test period was not due to practice.

Gait and ataxia of the left lower extremity were not tested as adequately as was line drawing, because if patients are made to move around too much and too many tests are performed the general disturbance and the factor of fatigue may impair the test on which the main attention is being focused (in this case, line drawing as a test of ataxia of the left arm).

Ataxia of the left lower extremity and imbalance of gait were found improved, but not normal, when the symptoms were retested about 2½ hours after the last flush on Jan. 25. This effect, of course, is too late to be of definite significance according to the standards employed. On arising on Jan. 26, the patient found gait and ataxia of the left lower extremity better than on the last test of Jan. 25 (overnight rest may have been a factor). It will be remembered that line drawing was also about normal on the morning of Jan. 26. Like line drawing, gait and ataxia of the left lower extremity are not known to have regressed subsequent to the flush of Jan. 26, although they may have done so transiently, coincidentally with line drawing, on the morning of Jan. 26.

Case 2.—H. C., a man aged 45, who had had multiple sclerosis for five months, showed visual and cerebellar impairment on examination.

Dr. Robert Coleman had found "areas of spasm in several arterioles in the right eye." A fixed absolute central scotoma had been plotted in the right visual field on nine examinations, between Oct. 17 and Dec. 9, 1949; it had gradually diminished in size until it almost disappeared.

On Nov. 11 a new peripheral relative scotoma was plotted. It was still present, though slightly smaller, on Nov. 15; one hour later, benzazoline (priscoline®) 50 mg., was injected subcutaneously; one hour after the injection the scotoma had disappeared. It was seen again on Nov. 22, when it was slightly larger, and was seen more faintly, and for the last time, on Nov. 29. It is true that the second examination was one hour, instead of a matter of minutes, after the injection, but the change is too striking to be ignored, especially in the presence of the evidence that the scotoma had been present for four days prior to the injection. The fixed central scotoma was unaffected by the drug (Fig. 3).

On Dec. 9, several new peripheral scotomas were found in the right visual field. These disappeared promptly after inhalation of amyl nitrite. The central scotoma had become very small; again it was unaffected by the drug.

Case 3.—I. P., a woman aged 50, had had multiple sclerosis for many years. The condition was still only moderately advanced, despite gradual regression of her condition for about two years. The situation had become stationary about eight months prior to observation.

About two months before observation a new attack occurred, with increase in unsteadiness of gait and in dragging of the right foot. A haze was reported to have appeared before the right eye at that time.

In the course of frequent ophthalmological examinations to check the possible effect of vasodilating drugs on slight visual-field defects, a right paracentral relative scotoma, which had not been present on Feb. 24 or Feb. 25, was found on Feb. 27. It disappeared promptly with the flush which followed the subcutaneous injection of 100 mg. of nicotinic acid (all injected nicotinic acid in this study was in the form of nicotinamide ["nicamin"]). It did not reappear in reexaminations one and four hours later, or on Feb. 29 or March 6 (Fig. 2).

The disturbance in gait improved transiently with each of many flushes, but, for reasons to be discussed later, this effect is not included as evidence.

Case 4.—J. O. B., a man aged 34, had had attacks and remissions of multiple sclerosis for about 10 years.

When observed in March, 1948, he had had weakness of the left lower extremity for six months. The left index finger and thumb had been numb for 30 days; the three ulnar fingers on the left hand had also been numb for 18 days.

Tetraethylammonium chloride was administered intramuscularly, with the results charted in Figure 2. The duration of vasodilation was not recorded, but the disturbing visual effect of the drug lasted only three to four hours, and this is probably near the limit of the autonomic effects of the drug.

About two weeks prior to these tests, the same drug had been used at Mount Sinai Hospital, with subjective improvement and improvement in appreciation of pinprick sensation in the left hand.

Case 5.—P. D., a woman aged 45, had had symptoms of multiple sclerosis at times for 24 years. A new attack had occurred 15 months before observation, leaving as residuals unsteadiness of gait and difficulty in focusing the eyes.

Four days prior to observation the unsteadiness of gait had suddenly become worse, because of increased ataxia of the right lower extremity. Vasodilation on four occasions, produced at

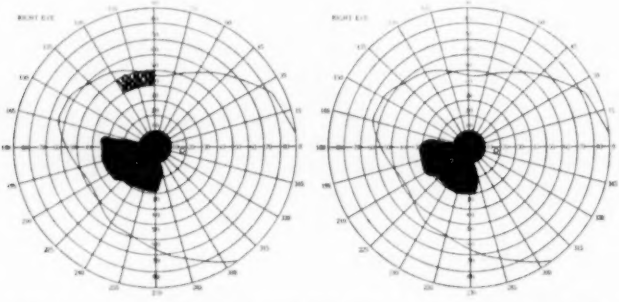

Fig. 3 (Case 2).—Visual field plotted with and without the peripheral scotoma, which disappeared after administration of benzazoline (priscol®).

first by nicotinic acid and later by histamine diphosphate injected subcutaneously, resulted in notable improvement in balance and in performance of the heel-to-knee test on the right side. The improvement lasted at first 1¾ hours, and later 4 to 6 hours. At the time of writing, the patient was receiving injections of histamine every six hours; this treatment appeared sufficient to keep her free from her most recent symptoms.

Case 6.—H. E., a woman aged 55, had had her first symptoms of multiple sclerosis 25 years before. The condition had been stationary.

For about five weeks the patient had experienced intermittent numbness and tingling of the three ulnar fingers of the left hand and the ulnar side of the hand and forearm, and intermittent tingling and constant numbness of all the finger tips of the right hand. Figure 4 shows succinctly the pronounced effects of vasodilation on these symptoms, as described subjectively by the patient. In particular, the duration of effects should be noted—days for some symptoms and weeks for others. All the symptoms were reported to have been absent from Jan. 21 up to the time of writing (March 24).

Absence of position sense from the right and left big toes was noted during the patient's stay in Mount Sinai Hospital from Dec. 20, 1951, to Jan. 8, 1952, and again on examination by Dr. Charles Ressler, on Jan. 12. Dr. Ressler injected 100 mg. of nicotinic acid intramuscularly on that date, and during the ensuing flush position sense was found to have returned to the

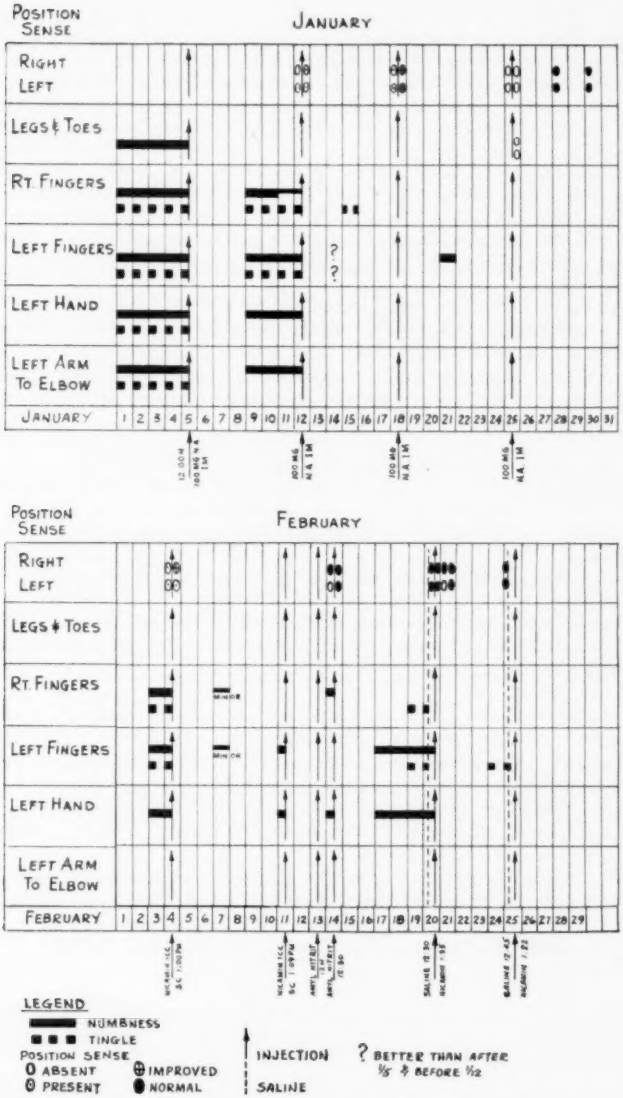

Fig. 4 (Case 6).—Coming and going of numbness and tingling and of position sense in January and February, 1952.

proximal joints of both big toes (Fig. 4). On Jan. 18, position sense was still present, but poor, in both big toes. Again, it improved with a flush produced by nicotinic acid. On Jan. 25, position sense was again absent from the right big toe and reduced in the left. Again, a flush elicited by nicotinic acid resulted in a return of position sense to normal in the right big toe and almost to normal in the left big toe. Repeated examinations since, up to the time of writing, have revealed normal, or nearly normal, position sense in both big toes. The findings concerning position sense are also charted in Figure 4. All this applies to the proximal joints: position sense had regularly been absent from the distal joints, where it has been unaffected by the vasodilations.

In association with these improvements in position sense, it is notable that the patient stated spontaneously that the sensation of movement in the feet had been absent, and that it returned with the first flush, on Jan. 5, since when it had been present at least most of the time.[28] (Position sense was not reexamined during or directly after this flush.)

Gait also improved markedly with each flush; again, for reasons given below, this is not included as evidence.

Subcutaneous injections of isotonic sodium chloride solution were given as placebos when the sensory symptoms of the hands were present, on Feb. 20 and 25. There was no effect on these symptoms or on gait.

Case 7.—H. Z., a man aged 30, gave a history of four years of symptomatic episodes of wide distribution both as to time and structures involved. Many scattered neurological abnormalities were found on examination.

Some details of the history could not be obtained with certainty; especially, the duration of incoordination of the left hand was unknown, though it was known that "numbness" of the hands had occurred intermittently over a considerable period and had persisted for several weeks each time.

Line drawing was done normally with the right hand but revealed moderately severe ataxia in the left hand.

On Jan. 31, 150 mg. of nicotinic acid injected subcutanously produced only a faint flush, and there was no change in the line drawing.

On Feb. 4, a heavy flush followed the subcutaneous injection of 150 mg. of nicotinic acid. This was associated with prompt and decided improvement to an approximately normal state. With minor fluctuations this improvement persisted through the last examination, on Feb. 11 (Fig. 2).

Cases 8 and 9.—The cases of R. A. and W. G., with chronic progressive disease, will be discussed later.

Case 10.[29]—A woman aged 33 had had intermittent symptoms for 10 years prior to the observation period. Visual symptoms had been progressive for two months.

Infusions of histamine diphosphate resulted in subjective improvement in vision each time that they were given. The duration of the effect was not noted. This patient had alternate filling and emptying of a single retinal arteriole.[30]

Case 11.[31]—On one occasion, not previously reported, a typical attack of visual impairment was shown (by plotting of the visual field) to be relieved immediately by inhalation of amyl nitrite. In another unreported instance a spontaneous attack of visual impairment disappeared (subjectively) within a few minutes of the start of a flush produced by nicotinic acid.

CONTROL FACTORS

One can never be completely certain of the reliability of clinical neurological findings, since absolute objectivity cannot be attained. Fatigue, feelings of well-

28. According to the patient, the symptom was an old one, in existence at least a year, but whether or not it had been intermittent is unknown. The duration of the loss of position sense as such is unknown.

29. Hitherto unpublished observations in Case 17 of Franklin and Brickner.[2]

30. Franklin and Brickner,[2] p. 145.

31. Case B of Franklin and Brickner.[2]

being, euphoria, hysteria, hope, despair, or malingering may alter the patients' responses and may impair the results even of visual-field tests. Practice in a test may improve a patient's ability to perform it. A special factor may disturb the interpretation of examinations of the motor system—apparent changes in strength or in ability to use an extremity may perhaps be due merely to changes in spasticity, and not to more fundamental factors, such as those involved in the pathogenesis of multiple sclerosis.

Efforts to control these factors as well as was feasible have been made. By one means or another, it is thought that all have been controlled to a certain degree.

Emotional Factors.—Use of Placebos: Isotonic sodium chloride solution or distilled water, instead of a vasodilating drug, was injected five times in each of two cases, with no effect. This method is not a perfect control because the patient is well aware that the flush, which he can plainly recognize when it occurs, is absent. However, the placebo was always given with an introduction describing its strong capacity to produce an "internal flush," all of its potency being exercised on the central nervous system, with none wasted on the skin.

Variations in Degree of Flush: In six instances, in three patients, the drug failed to produce a noticeable flush, and there was no improvement in function. Greater and less intensities of flush were also observable at least six times in six other patients. In all, the degree of improvement appeared to be commensurate with the intensity of the flush. These observations would seem to be a better control than the use of placebos. In summary, at least 12 observations of this type have been made on 9 patients.

Practice Effects.—These are considered controlled by the fact that improvement in line drawing was followed by regression at least once in all but one case (Case 7). In Case 1 practice effects were fairly well excluded by other means (see above). Practice does not seem to be an issue in any of the other tests employed in the current observations.

Spasticity.—It is difficult, if not impossible, to control this symptom by clinical examination when muscular movement is being tested. Even tremor, like that appearing in line drawing, may possibly be influenced by spasticity. For this reason, mention has not been made of improvements in motor function unless they became permanent, except in Case 5, in which there was only cerebellar ataxia. There were many transient improvements in motor function, chiefly in gait. The only other improvements in motor function which were included are the line drawings in Cases 1 and 7. These improvements have been long-lasting and hence, presumably, are to be regarded as representing changes in the central nervous system related to the disease itself, rather than merely changes in neuromuscular function.

Regularity of Effects.—The almost uniform regularity of results also would seem to be a controlling factor. In addition, the fact that a number of observers have by now seen all the various manifestations described is of value as confirmation, and therefore probably as a type of control.

Differential Improvement.—Only some symptoms, almost always known to be new ones, improve; others, usually old ones, do not improve. This fact seems helpful as a control; if the improvements were emotional in nature, more inclusive improvement might be expected.

CASES OF CHRONIC PROGRESSIVE DISEASE

The results described so far refer to acute episodes. Some of the episodes have had a probable chronic progressive background (Cases 6 and 7, and possibly Cases 3 and 5).

Cases 8 and 9 (R. A. and W. G., respectively) are cases of advanced chronic progressive disease without acute episodes. If the substance of this communication is correct, it may be possible to check a progressive course, and perhaps to produce some degree of improvement in the patient's symptomatic status. In both these cases there is some evidence that these results have occurred.

The observations in both cases are complicated, however. In some of the trials, gross control of the placing and size of drawn lines and of the shape of angles and circles, was obviously improved with the vasodilation, but the lines themselves were more wavy and tremulous, indicating an increase in fine tremor of the fingers. Neither patient showed a uniform repetition of this effect with every test; it occurred only at times. In Case 8 increase in head tremor occurred oftener than not throughout the visible flush and was exactly coincidental with it. In both cases there was evidence, suggestive but not conclusive, that these increases occurred chiefly when the flush was very intense, but not otherwise.

Another patient (Case 3), with weakness of the right lower extremity, had great difficulty in getting the right heel onto the left knee when tested; she was able to slide the heel down the shin with little or no ataxia, however. During flushes she moved the extremity much more freely, reaching the knee far more easily, but showed considerable ataxia in moving the heel down the shin. If the increase in ease of movement was due to decrease of spasticity, which is not at all certain, the suggestion would be that tremor might become more visible if spasticity is lessened. Such a supposition might explain the events just described in Cases 8 and 9.

R. A. (Case 8) added the explanation that, more than the other drugs, nicotinic acid "peps me up." He felt that it relieved spells of overpowering fatigue to which he was subject, and even ordinary fatigue. Hence, he felt more like cooperating, and did better line drawing, during nicotinic-acid flushes. Histamine flushes had no definite effect; yet amyl nitrite flushes did have a slight beneficial effect, and a single trial with papaverine hydrochloride had a very pronounced beneficial effect.

So far as could be determined, factors like these did not arise in the cases of acute episodes, in all of which the disease was less advanced. The results of the tests in those cases seemed relatively uncomplicated and acceptable. The massiveness of involvement of the central nervous system in Cases 8 and 9 may well have complicated the results of tests.

Clearly, the observations suggest that, at least in advanced cases, vasodilation therapy may not be without danger.

POTENTIAL FAILURES OF NEW SYMPTOMS TO IMPROVE

Assuming that the theories and approaches reported here are correct, an unknown proportion of failures of symptoms to respond should still be anticipated, for the following reasons: 1. First phenomena in patients not previously known to have had multiple sclerosis may not be treated while still reversible, especially if the symptoms are slight and have not been seen by a physician or correctly diagnosed. 2. Patients known to have multiple sclerosis, although warned of the

need to regard new symptoms as emergencies to be reported at once, may nonetheless procrastinate. In the current series, patients have postponed report and treatment up to as long as a week, for a variety of stated reasons. An important "reason," against which patients should be warned, is doubt concerning whether a phenomenon is a definite symptom of the disease. Treatment should be given within minutes even if there is doubt. 3. Paradoxical effects of vasodilating drugs have been described; retinal arterioles have been observed to constrict instead of dilate.[2] Forbes, Wolff, and Cobb,[32] many years ago, described paradoxical effects following histamine infusions in cats. Such paradoxical effects may be expected to occur at times in some patients. Under these conditions, the symptom would regress instead of improve. Confusion might be caused by the occurrence of the regular effect in some blood vessels and a paradoxical effect in others. 4. Some attacks of the disease may, perhaps, progress so fast that tissue death, possibly by thrombosis, may occur before treatment can be started. 5. Anoxia may increase, instead of decrease, in the central nervous system, as a result of rapid lowering of peripheral blood pressure.

SUGGESTED TREATMENT PROGRAM

The following treatment program for acute episodes is suggested:

1. The response of the new symptoms to vasodilation should be tested. The test should be made as soon after the onset of the symptom as possible.

2. If the symptom responds, one should learn how long the effect endures, regardless of the duration of the flush.

3. A schedule of administration of vasodilating drugs, shown to be effective in the patient under study, should be set up. The administration should be so timed that each dose is given prior to the time at which the symptomatic effect of the previous dose is expected to disappear. Doses may have to be given during the night.

4. One should be ready to change the timing of doses if the symptom begins to reappear sooner than expected (this has not yet actually been observed).

5. Patients should be trained in self-administration of an effective vasodilating drug, so that immediate treatment can be started if a new symptom occurs. They may keep an iontophoresis apparatus at home and at their place of work and carry in their pockets drug preparations to take sublingually, orally, or by inhalation within a matter of seconds.

6. Anticoagulation measures should be instituted the moment activity of the disease appears, and should be maintained as long as vasodilation treatment is continued.

7. Very frequent, detailed observation of the course of each symptom under study is essential. Routinization of treatment is not to be considered at present, and one should not attempt to use this plan unless prepared to follow the course of events meticulously.

8. An ophthalmologist's services are indispensable. He should be able to spread his studies over considerable periods during the day, so that observations before and after drug administration may be made and the duration of effects noted. Frequent observation of the retinal blood vessels is, of course, also important. Fundus

32. Forbes, H. S.; Wolff, H. G., and Cobb, S.: Cerebral Circulation: X. Action of Histamine, Am. J. Physiol. **89**:266, 1929.

photography may also be helpful, and should be available with sufficient freedom that pictures may be taken repeatedly over periods of hours, on any indicated day or time of day.

9. All the early tests of drugs, and as many of the later ones as possible, should be made with concomitant blood-pressure evaluations, and with the use of drugs to offset the effects of the vasodilators in case of faintness or sudden regression. Especially with advanced cases, it may be wise to make the early tests with the patient prone.

This treatment plan is suggested for acute episodes whether or not they occur on a chronic progressive background.

In cases of chronic progressive multiple sclerosis without acute episodes, anticoagulation therapy at least would seem indicated. Vasodilation treatment has not yet been adequately investigated in such cases, but study is in progress.

COMMENT

The possibilities mentioned earlier, i. e., that tissue death may occur as a result of thrombosis and that anoxia may be increased by peripheral vasodilation, suggest that anticoagulation therapy should be added at any time the disease process is thought to be active, and throughout whatever period vasodilation treatment is under way. This would tend to reduce the risk of occurrence of thrombosis prior to the establishment of the proper time schedule for vasodilation treatments.

Putnam has long urged the use of bishydroxycoumarin,[33] and he reported a series of 43 cases in which it was used for periods up to eight years, in only one of which an acute relapse occurred during treatment. It is suggested that there would seem to be an especially distinct need for the drug during acute attacks, and in cases of relapse, in order that exacerbations should be avoided. Putnam,[4] who first noted thrombi in vessels near lesions in multiple sclerosis, sought a cause for them in an abnormal state of the blood, but did not find a definitive abnormality. Certain abnormalities have been described, however.[6] The vasospasm discussed in this and in other communications could also well be a cause.

Vasodilation supposedly does not affect the basic etiological factors of multiple sclerosis but, according to the theory, acts only on the factors mechanically responsible for the lesions. Hence, at most, treatment with vasodilation can do no more than cause symptoms to disappear, and then hold them in check until the etiological factors have gone out of action. Treatment must, therefore, be continued until cautious testing shows that activity of the disease process is over and that the symptoms do not return.

An extensive review of therapeutic attempts in multiple sclerosis was made in 1936; it showed how easy it is for workers to be misled in estimating therapeutic results.[34] One of the current attitudes toward multiple sclerosis is based on this tendency of the disease to mislead its therapeutic students; many believe that no

33. Putnam, T. J.; Chiavacci, L. V.; Hoff, H., and Weitzen, H. A.: Results of Treatment of Multiple Sclerosis with Dicoumarin, Arch. Neurol. & Psychiat. **57**:1-3, 1947. Putnam, T. J.: The Treatment of Multiple Sclerosis: Multiple Sclerosis and the Demyelinating Diseases, A. Res. Nerv. & Ment. Dis. Proc. **28**:585, 1950.

34. Brickner, R. M.: A Critique of Therapy in Multiple Sclerosis, Bull. Neurol. Inst. **4**:665, 1936.

therapeutic work will be reliable until the fundamental causes of the disease are known. The present study is presented with full recognition of all this, and with all of the caution called for by that recognition. It is thought, nonetheless, that the plan should be put forward, so that others may test it. The therapeutic approach suggested, however, is more than a symptomatic one, even though it is not related to fundamental causes; it is based on a theory of the pathogenesis of the lesions, and this theory is founded on the actual observation of retinal vasospasms associated with scotomas.

Another question is whether the phenomena affected by the drugs are part of the essential picture of multiple sclerosis or are side-effects. They are typical phenomena of the disease and are what patients suffer from; hence they must be considered an essential part of the disease picture.

A comment is necessary concerning the modus operandi of the vasodilating drugs which have been employed. Some investigators have used histamine with the idea that it counteracts an allergic state, which they believe important in the etiology of multiple sclerosis. The evidence assembled in this communication suggests, however, that the action is entirely a vasodilating one, since a considerable variety of drugs other than histamine have been used, all equally effective (amyl nitrite, papaverine hydrochloride, nicotinic acid, benzazoline, and tetraethylammonium chloride).

Another aspect of the subject should be introduced for completeness of discussion. Additional reasons exist to support the idea that the vascular system plays a role in production of lesions; one of these is the suddenness of onset of attacks, both major and minor.

The observation of Brickner and Franklin from which arose most of the studies referred to was the precipitation by a hot bath of constriction of retinal arterioles associated with multiple scotomas.[1] Similar phenomena were sought and found without difficulty in other patients. (This observation, in turn, had been preceded by Franklin's finding of sudden transient retinal blanching, with transient blindness, in a case of undiagnosed disseminated neurological disease.[35] This patient subsequently stated that emergence from darkness into a very strong light sometimes precipitated his attacks of blindness.) The observations suggested that one way in which the lesions of multiple sclerosis might increase and advance was through vasospasms. The theory was evolved that the vasospasms might sometimes be elicited by reflex action, evoked by various stimuli, such as heat in the form of baths, food, and hair dryers.[3a,b] The observations on the effects of heat on symptoms have been confirmed by Bente and Betz [12] and by Guthrie,[36] who contributed additional interesting data and discussion.

SUMMARY

Three standards are presented which may be of use in evaluating the therapeutic effect of rapidly acting drugs in multiple sclerosis. It is thought that these standards make the problem of spontaneous remissions less difficult to deal with.

35. Franklin, C. R.: Paper presented at a meeting of the New York Academy of Medicine, Section of Ophthalmology in 1943.

36. Guthrie, T. C.: Visual and Motor Changes in Patients with Multiple Sclerosis, A. M. A. Arch. Neurol. & Psychiat. **65**:437, 1951.

These standards are employed in evaluating the symptomatic effects of rapidly acting vasodilating drugs. This type of drug is selected for testing on the basis of earlier observations which indicated that many symptoms are reversible for a time and that vasodilation could induce their reversal.

The effects of these drugs seem to meet the standards described. Many symptoms known to be new have been reduced or abolished within a few minutes of the onset of a drug-induced flush. In some cases the symptom has remained absent as long as the patient continued to be observed (several days or weeks). In other cases the symptoms have returned, again to be reduced or abolished a few minutes after the onset of the flush. Hence it is believed that reversible symptoms have been affected favorably, predictably, and repeatedly by vasodilation.

The basic phenomenon of apparent reversibility by vasodilation has been seen at least 134 times, in 34 cases, by four separate observers, and it is thought of as reasonably soundly grounded.

Previously, the course of single symptoms in relation to vasodilation had not been followed meticulously and in detail. The duration of relief following a single vasodilation had never been known. It was mistakenly assumed that the duration of improvement was coincident with the duration of the flush, and that 24-hour-a-day vasodilation would be necessary over very long periods for the achievement of any therapeutic benefit. It has now been found that improvement may last several days or longer after a single flush.

The duration of improvement has been timed and the course of single symptoms followed meticulously 32 times in 9 cases.

A program of therapy, based on these observations and containing nine points, is suggested. Frequent detailed observations on the course of the symptom being studied are essential. The observations and suggestions refer only to the management of new, acute episodes. Certain dangers in the therapeutic procedure are noted.

Dr. William Toll and Dr. David Hays assisted in performing the ophthalmological examinations and determining the neurological state of the patients; Miss Gertrude Clark helped in the general conduct of the investigation; Mr. John Sheldon made Figures 2 and 4, and Miss Marian Richter assisted in preparing the manuscript.

USE OF DIMERCAPROL IN TREATMENT OF PERIPHERAL NEURITIS

A Further Study

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AFTER it had been demonstrated that dimercaprol injection U.S.P. (BAL) (2, 3-dimercaptopropanol) was an effective agent in the treatment of arsenical poisoning and polyneuritis, its use in the treatment of alcoholic and diabetic polyneuritis was reported by Furmanski.[1] Although the recommended doses in the treatment of heavy metal poisoning have been in the range of 3 to 5 mg. per kilogram of body weight every four hours, given in short courses, with later decreased doses,[2] Furmanski used small doses of dimercaprol for longer periods. Whereas in arsenic poisoning the largest nontoxic dose is used for maximum increase in urinary excretion of arsenic,[3] in the treatment of alcoholic polyneuritis an enzymatic action of dimercaprol was postulated. The four patients in the series did not respond to large doses of crude liver and vitamins, but did respond to daily doses of dimercaprol of approximately 1.5 mg. per kilogram of body weight. The dimercaprol was given for from 9 to 22 days. This response to small doses of dimercaprol was considered indicative not of a deficiency state but of a biochemical inability to use "already present materials." Another patient, who suffered from infectious mononucleosis and polyneuritis with facial diplegia, was treated with dimercaprol by Creaturo.[4] The dosage schedule followed was that recommended by Furmanski.

Nielsen has reported favorable results with dimercaprol in 10 cases of "so-called neuronitis" (polyneuritis with facial diplegia, infectious neuronitis, or the Guillain-Barré syndrome.[5] In each of five of the cases the polyneuritis was associated with alcoholism and macrocytic anemia, nasal diphtheria, gold injections and mephenesin (tolserol®), diabetes, and an acute infection, respectively. In the remaining five cases the onset was unassociated with any of these possible causative factors. In

From the Neurological Section, Veterans Administration Hospital, Bronx, N. Y.

1. Furmanski, A. R.: BAL Therapy of Severe Peripheral Neuropathies, Arch. Neurol. & Psychiat. **60**:270 (Sept.) 1948.

2. Longcope, W. T., and Luetscher, J. A.: The Use of BAL (British Anti-Lewisite) in the Treatment of the Injurious Effects of Arsenic, Mercury, and Other Metallic Poisons, Ann. Int. Med. **31**:545 (Oct.) 1949.

3. Wexler, J.; Eagle, H.; Tatum, H. J.; Magnusen, H. J., and Watson, E. B.: Clinical Uses of 2,3-Dimercaptopropanol (BAL): II. The Effect of BAL on the Excretion of Arsenic in Normal Subjects and After Minimal Exposure to Arsenical Smoke, J. Clin. Invest. **25**:467 (July) 1946.

4. Creaturo, N. E.: Infectious Mononucleosis and Polyneuritis (Guillain-Barré Syndrome): Report of a Case of Facial Diplegia Treated with 2,3-Dimercaptopropanol (BAL), J. A. M. A. **143**:234 (May 20) 1950.

5. Nielsen, J. M.: The Use of BAL in Neurology, Bull. Los Angeles Neurol. Soc. **15**:43 (March) 1950; Treatment of Neuronitis with BAL, ibid. **15**:61 (June) 1950.

describing his dosage schedule, Nielsen advocated larger amounts of dimercaprol. The single dose recommended was 2.5 mg. per kilogram of body weight. This dose was given approximately four times a day for two days, twice a day for two days, and once daily for varying periods up to a month.

In five of Nielsen's cases there was little evidence of improvement from use of dimercaprol. In Case 10 the condition improved after the drug was discontinued. In Case 7, in which dimercaprol was reported to be of benefit, death occurred two days after treatment was begun. In Case 5 the patient was still using a respirator at night four months after treatment. In Case 6, one of postdiphtheritic polyneuritis, four months was required for recovery. In Case 8 the patient's condition was described as "not improved."

Of the five cases in which improvement occurred during dimercaprol therapy, four were in the group in which the disease came on without known relation to any of the above-mentioned etiological factors. One patient was alcoholic with macrocytic anemia. All these patients seemed to recover slowly from their polyneuritis, recovery requiring 10 days to 6 months. Whether there was any therapeutic value in the dimercaprol cannot be stated from this evidence, because recovery is the expected result in this disease. Some patients seemed to get worse when dimercaprol therapy was discontinued, until it was restarted. However, during these periods without treatment, the patient usually had a "cold abscess" in the gluteal area, requiring discontinuation of therapy.

In a report on 22 patients with diabetic neuritis, Schneider[6] gave doses of dimercaprol, as advised by Furmanski, in the range of 100 to 200 mg. a day. Of the 22 patients, 12 were reported as showing "definite improvement." By "improvement" was meant the report by the patient that pain, numbness, burning, and paresthesiae had become less severe during dimercaprol therapy. There were no changes recorded in motor performance, reflexes, or sensory status. Five patients had a recurrence of their symptoms in 2 days to 10 months. No serious toxic reactions were described. An interesting observation was the exacerbation of pain in the extremities immediately following each intramuscular injection of dimercaprol.

In the present study dimercaprol has been administered to 18 patients, in an attempt further to determine its therapeutic value in various forms of polyneuritis.

METHOD

Patients were chosen from admissions to the neurological service of a Veterans Administration Hospital and a large city hospital. Two patients were selected from private neurological practice. The only criterion used for selection was that the patient show evidence of peripheral neuritis on neurological examination.

The dimercaprol was administered as a 10% solution with 20% benzyl benzoate U. S. P. and peanut oil U. S. P. as the base.

Each patient had a complete examination, general and neurological, at the beginning and at the end of dimercaprol therapy and on the designated follow-up dates. The patients were aware that they were receiving dimercaprol injections.

To evaluate the statistical significance of the associations between the pairs of characteristics studied, Fisher's direct method for obtaining the probability that a given degree of association

6. Schneider, R. W.: The Use of British Anti-Lewisite in the Treatment of Diabetic Neuropathy, Cleveland Clin. Quart. **17**:197 (Oct.) 1950.

is a function of chance alone was used.[7] The *P* value which results gives directly the probability that as great a degree of association as was obtained could have occurred by chance alone. According to a common statistical convention, when this value is less than 0.05 (5 chances in 100, or 1 in 20), the hypothesis of chance association is rejected, and the association is accepted as significant (or real, i. e., not a function of chance alone). The statistical data are included in the next section.

RESULTS

History, Physical Examination, and Laboratory Findings.—A summarized case report of each patient appears in the accompanying table.

Of the 18 patients, 17 were men. Their ages ranged from 24 to 63.

Six of the 18 patients had had a previous attack similar to their present episode. Sixteen of the patients presented so-called predisposing factors in various combina-

Clinical Data on Eighteen Patients with Peripheral Neuritis Treated with Dimercaprol

Patient No.	Age, Yr.	Duration of Present Attack	Spinal Fluid Protein, Mg./100 Cc.	Dimercaprol, Total Dose, Mg./Kg. of Body Weight	Length of Dimercaprol Course, Days
1	63	3 mo.	61	57	22
2	52	2 wk.	200	68	24
3	51	3 wk.	157	77.5	31
4	56	4 mo.	206	55	22
5	47	3 mo.	356	65	26
6	32	1 mo.	246	37.5	15
7	25	2 wk.	420	24	5
8	31	6 mo.	206	66	14
9	34	2 yr.	Normal	108	29
10	24	1 yr.	Normal	40	10
11	44	1 yr.	66	164	18
12	45	3 wk.	Normal	52	10
13	37	1 wk.	Normal	36	24
14	60	3 yr.	130	45	8
15	34	1 yr.	Normal	114	30
16	49	8 days	220	13	12
17	55	2 wk.	410	63.5	16
18	33	1 wk.	85	99	21

tions. These included alcoholism (seven), diabetes (three), recent acute infection (four), dietary deficiency (three), cirrhosis (two), diphtheria (one), sensitivity reaction to sulfadiazine (one), operation (one), leukemia (one), cortisone therapy (one), and encephalitis (one). Alcoholism and cirrhosis were associated twice; diabetes and alcoholism twice.

The length of the present episode ranged from one week to three years. The attacks of nine patients had lasted less than one month at the time of admission; five patients were symptomatic for one to three years.

No patient complained of arm symptoms alone at the time of admission; 10 patients had both arm and leg symptoms; 8 patients had leg symptoms only. The age of the patient (over or under the median age of 42) was not significant in terms of whether or not the patient had arm or leg symptoms at the time of admission (*P* value more than 0.05). Similarly, there was no significant correlation

7. Fisher, R. A.: Statistical Methods for Research Workers, Ed. 6, Edinburgh, Oliver & Boyd, Ltd., 1936.

between the involvement of the upper and lower extremities and the duration of the present illness (P value greater than 0.05). However, the patient with a previous episode of neuritis was likely to be admitted with leg symptoms only (P value 0.014).

There were no striking findings on general physical examination except that five patients had hepatomegaly, three of whom were alcoholic.

Neurological examination revealed that 15 patients had dysfunctions of all four extremities; 3 patients, of the legs only. Apparently, five patients had abnormalities of the arms on neurological examination, of which they had not complained. Other abnormalities observed were facial weakness (four), palatal weakness (three), sensory levels (two), optic nerve atrophy (two), disorientation and memory loss (two), ataxia (two), and paraplegia with urinary and fecal incontinence (one). The neurological findings were those typically of peripheral neuritis.

The spinal fluid protein was increased in 13 of the 18 patients.

Of the five patients with normal spinal fluid protein levels, four were alcoholic (two with cirrhosis). There was no stastistically significant relation between the level of the spinal fluid protein and the presence or absence of a previous attack of neuritis (P value greater than 0.05), between the level of spinal fluid protein and whether the patient reported involvement of all extremities or of legs alone on admission (P value 0.176), or between the level of spinal fluid protein and whether the present illness had a duration of more than six months (P value greater than 0.05). However, the patient with neurological signs in the legs only at the time of admission was likely to have a normal spinal fluid protein (P value 0.025).

Previous Therapy.—In these 18 patients, no improvement was observed with dietary therapy (18), parenteral use of vitamins (18), control of diabetes (3), antibiotic therapy (5), administration of vitamin B_{12} U.S.P. (2), and use of cortisone (1).

Dimercaprol Treatment.—The various schedules for giving dimercaprol have been described. To these 18 patients dimercaprol was given by deep intramuscular injection. The number of days dimercaprol was given varied from 5 to 31 days, with an average of 18 days. The total daily dose varied from 1.5 to 16 mg. per kilogram of body weight.

Designating 1 unit as 1 mg. per kilogram per day, Furmanski suggested a course of therapy of 45 units; Nielsen, a course of 95 to 160 units. Nielsen's results, however, were declared as "good" even on much less than 95 units. Within this frame of reference, six patients have been treated by Furmanski's schedule, four by Nielsen's schedule, and eight by a dosage schedule somewhere between the two.

Results of Treatment.—Although there were no demonstrated toxic effects from the dimercaprol which required the cessation of treatment, five patients had pronounced gluteal pain and tenderness.

Of the 18 patients, 4 reported improvement during treatment. However, the neurological findings were improved in only two patients. One of these patients continued a slow, gradual improvement begun before dimercaprol treatment, receiving 24 units of the drug, one-half the amount recommended by Furmanski. One patient who received 13 units showed a slight increase in vibration sense in the arms.

Seven patients became worse during and immediately after dimercaprol therapy, as judged by neurological examination. During the treatment period, two subjects had onset of atrophy in the shoulder girdle, and arms and legs, respectively

Increased weakness in the extremities was manifested by two patients; increased ataxia and difficulty in walking, by one; increase in areas of sensory loss, by two, and increase in leg pains, by two.

In addition to the seven patients who became worse during or immediately after dimercaprol therapy, nine showed no change with treatment. In this group are the four patients who were treated in the manner of Nielsen. Since there was no statistically significant improvement with dimercaprol, it made no difference whether Nielsen's dosage was used or not (P value greater than 0.05).

Follow-Up Results.—The periods of observation ranged from 4 to 52 weeks. At the time of follow-up neurological examination, 10 patients had evidence of improvement. This improvement occurred in eight patients anywhere from 1 to 24 weeks later, or an average interval of 8.8 weeks after treatment with dimercaprol. Two of these 10 patients, as previously indicated, showed minimal improvement during the therapy period.

Eight patients improved neither during therapy nor by the time of follow-up study. These follow-up examinations were done 4 to 52 weeks after treatment, at an average of 21 weeks.

Of the two groups, i. e., the 10 patients who eventually showed improvement and the 8 patients whose condition had not improved, there was no significant correlation in either with age (P value greater than 0.05) or duration of present episode (P value greater than 0.05). However, the eight who failed to show improvement were the eight who complained only of leg symptoms on admission. The patient who complained on admission of symptoms in the legs and not the arms was found to have a poor prognosis (P value 0.000046).

Among this group of eight patients with a poor prognosis were the three who complained only of leg symptoms and showed no arm dysfunction on examination. Among the eight who did not show improvement were five of the six patients with a previous attack of peripheral neuritis.

However, there was no statistically significant relation (P value greater than 0.05) between follow-up results and the following characteristics: age (over or under 42); duration of present attack; presence or absence of arm and leg involvement on neurological examination; level of spinal fluid protein; whether or not the patient received dimercaprol, and whether or not he was treated by Nielsen's dosage. A poor follow-up result was significantly related to a previous episode (P value 0.014) and the presence of leg complaints only on admission (P value 0.000046).

COMMENT

The theoretical basis for use of dimercaprol in peripheral neuritis has been adequately discussed by Furmanski [1] and Nielsen.[5]

In this experience with 18 patients, there has been no evidence that dimercaprol, whether used in large or small doses, has favorably influenced the course of peripheral neuritis. In this group have been included patients with "neuronitis," according to Nielsen's standards. These patients, similarly, have not appeared to respond to dimercaprol therapy with significant improvement. Many of these patients with peripheral neuritis have been made worse during and immediately after dimercaprol. Evidence for this has been a definite increase in neurological findings (atrophy, weakness, ataxia, and sensory loss). When, as occurred with 10 persons,

a patient did improve, he did so, on the average, eight weeks after the dimercaprol injections had been stopped. It was difficult to ascribe such a delayed good result to the dimercaprol therapy.

A statistical evaluation has shown that few relationships between the various clinical characteristics of these 18 subjects were significant. However, the probability that a patient who has had a previous attack and complains of leg symptoms only at the time of admission will have an unfavorable follow-up is significant.

SUMMARY

Dimercaprol U. S. P. (BAL) has been administered to 18 patients with peripheral neuritis. Various doses have been given.

From evaluation by symptoms and neurological examination, there is no evidence that dimercaprol has favorably influenced the course of this disease. Seven patients were made worse during dimercaprol therapy.

In this group of 18 patients, a classification according to age, duration of illness, predisposing factors or diseases, level of spinal fluid protein, or response to therapy has been of no significant clinical value.

No patient who complained of only leg symptoms at the time of admission showed improvement.

The patient who had had a previous attack of neuritis was likely to have a poor prognosis.

Room F-636, New York Hospital.

Jacob Cohen, Ph.D., of the Department of Psychology of the Veterans Administration Hospital, Bronx, N. Y., assisted in the statistical evaluation of these data.

Case reports have been made available by Dr. Julius Wolf, Section Chief in Medicine; Dr. Abraham Jacobson, Section Chief in Medicine, and Dr. Laurence Kaplan, Attending Physician in Neurology, all of the Veterans Administration Hospital.

PREFRONTAL LOBOTOMY

Analysis of Results in One Hundred Twenty-Two Cases in a State Hospital

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A PREFRONTAL lobotomy program was initiated at Binghamton State Hospital in the spring of 1946. We report the results obtained in 122 cases of lobotomy performed by the Freeman-Watts standard method up to the end of 1950. The patients reported have been observed from five years to six months since operation. The accompanying chart shows the rapid yearly increase in the number of lobotomies performed in this institution, which operation has now become our most important tool in the treatment of chronic mental illness.

MATERIAL

The 122 patients reported all had chronic mental disorders. With a few exceptions, all had been unsuccessfully treated with one or several of the accepted shock methods, and prior to the introduction of lobotomy their prognoses were considered hopeless. As in every state hospital series, the major portion of the patients represented the schizophrenic group, 106 of the 122 being in that group. The remaining groups of patients were too small to allow significant statistical conclusions. The psychoses represented were as follows: postencephalitic psychosis, six patients; psychoses with mental deficiency and episodes of excitement, four patients; involutional psychosis, five patients, and manic-depressive psychosis, one patient. Ninety-five patients were females and 27 males; 4 were Negroes, and the rest were white persons. The ages ranged from 17 to 66. The duration of the psychoses ranged from 1 to 50 years.

RESULTS

In order to analyze the results, we have divided the patients into nine categories, based principally on the degree of social adjustment:

Group 1: Patients discharged with good social adjustment.

Group 2: Patients placed under convalescent or family care. These gained satisfactory social adjustment, but are in need of some supervision. Several are expected to be finally discharged.

Group 3: Patients who show much improvement and can be kept in an open ward and given ground parole. They are not quite well enough for extramural life

Group 4: Patients who show improved behavior, with loss of assaultiveness, but must be kept in the closed ward.

Group 5: Patients with slight improvement.

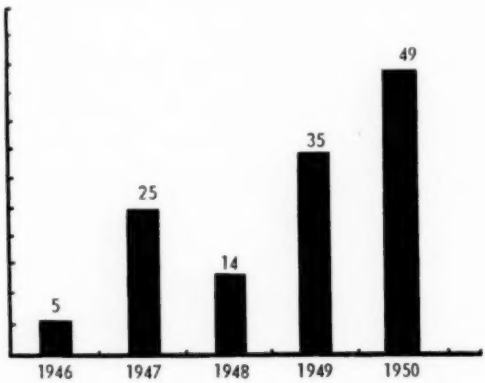
Group 6: Patients whose condition is unchanged.

Group 7: Patients who relapsed after an improvement of short duration.

Group 8: Deaths due to lobotomy.

Group 9: Deaths due to other causes.

The results are summarized in Table 1. Of the entire series, 63% benefited by the operation to some degree, and 42.5% of this 63% benefited to a considerable degree. As previously noted, numbers in the nonschizophrenic groups are too small to bear statistical significance. It is our impression that the so-called affective disorders as a rule respond very favorably to lobotomy. In the cases of involutional psychosis age and general health may constitute a hazard, but we feel that an agitated, paranoid patient with an involutional psychosis has everything to gain by operation. It would appear inhuman not to operate on such a patient, just for fear of spoiling



Yearly increase in lobotomies.

the mortality statistics. In cases in which there may be advanced cerebral arteriosclerosis, it may be advisable to obtain a pneumoencephalogram before operation in order to determine possible cortical atrophy, the presence of which would contraindicate lobotomy. Psychoses with mental deficiency of moderate degree, with episodes of excitement and aggressive, disturbed behavior, seem to respond satisfactorily, and the patient can be transformed into a rather pleasant, harmless person. One of our patients could be placed in family care, whereas in cases of low-grade mental deficiency, with long-standing psychotic manifestations, the results are not encouraging. The postencephalitic group showed considerable benefit. The postencephalitic psychosis is unique in that it seems to be the only one of the so-called organic psychoses that responds favorably to psychosurgery.

Among the schizophrenic patients, the best results were obtained with the catatonic group. The second best results were in the hebephrenic group, with the paranoid group taking third place. In this series, the incidence of patients showing no change was lowest, and the number with relapses was highest in the hebephrenic

TABLE 1.—*Synopsis of Cases of Lobotomy from 1946 to 1950*

Result	Schizophrenia								Manic-Depressive Psychosis		Involutional Psychosis		Mental Deficiency with Emotional Instability	Postencephalitic Psychosis		Total	Total No. Cases, %
	Catatonic	Relobotomy	Hebephrenic	Relobotomy	Paranoid	Relobotomy	Simple	Relobotomy	Depressed	Manic	Melancholia	Paranoid			Relobotomy		
Discharged	5	1	7	..	1	..	0	..	0	1	2 S 1 *	2	0	1	..	19	15.5
Convalescent care or family care	7 S 1	..	4	1	4	..	0	..	0	0	0	0	1	0	..	16	13
Much improvement; open ward; ground parole	5	..	4	..	5	..	1	..	0	0	0	0	1	1	..	17	14
Improvement; closed ward	10 S 1	..	10	1	6 S 1	1	0	..	0	0	0	0	0	0	..	26	21.5
Slight improvement	1	..	6	..	4	..	0	..	0	0	0	0	0	1	..	12	10
No change	5	1	1	..	8	..	0	..	0	0	0	0	1	1 S 1	..	16	13
Relapse after improvement for short time	1	..	4	..	1	..	0	..	0	0	0	0	0	1	..	7	5.5
Death after lobotomy	1	..	2	..	2	..	0	..	0	0	0	0	1	0	..	6	5
Death from other causes	0	..	0	..	1	..	0	..	0	0	0	1	0	1 S 1	1	3	2.5
Seizures	2	..	0	..	1	..	0	..	0	0	1	0	0	2	..	6	5
Total no. cases	35	2	38	2	32	1	1	..	0	1	2	3	4	6	1	122	....
Total no. operations	37	..	40	..	33	..	1	..	0	1	2	3	4	7	..	128	....

* S indicates seizures.

group. We shall return later to the question of the type of schizophrenia as a prognostic criterion.

Of the six postoperative deaths, two were attributed to hemorrhage, one to brain abscess, and one to the basilar type of acute meningitis; in two cases no autopsy was performed.

When there was no complication, most patients left the hospital ward at the end of one week.

COMMENT

In this discussion, consideration is restricted to the schizophrenic group. Unquestionably, since the introduction of shock treatment the total number of patients with chronic schizophrenia in state hospitals has not diminished. Shock therapy apparently has been able only to hasten recovery in patients who eventually would have recovered spontaneously. Prefrontal lobotomy has contributed significant therapeutic results in large series of cases in which treatment with all forms of shock therapy had failed. It should be noted that this is true for occasional shock-resistant affective disorders. In this connection, there arises the question whether a criterion can be established which would give an important prognostic clue to the probability of benefit from lobotomy. Other authors have stated that the type of schizophrenia is a most important prognostic criterion,[1] claiming that the best results are obtained

TABLE 2.—*Diagnosis (Schizophrenic Type) and Result*

Result	Catatonic	Hebephrenic	Paranoid	Total Group
Discharged, %	14	18	3.2	15.5
Convalescent care and family care, %	20	10.2	12.8	13
Much improvement, %	14	10.5	16	14
Total patients considerably improved, %	48	38.8	32	42.5

in cases of the paranoid and catatonic type and that patients with the hebephrenic and simple types were rather resistant to lobotomy. Others have reported the best results in the catatonic group, less favorable results in the paranoid group, and the poorest results in the hebephrenic group.[2] We found the best results in the catatonic group, the next best in the hebephrenic group, and the least favorable in the paranoid group. In our series, the hebephrenic group showed the highest number of discharges, but also the highest number of relapses. The condition of only 1 of 38 patients in the hebephrenic group appeared unchanged, as compared with 8 of the paranoid group (Table 2). We are inclined to consider the descriptive classification as inconclusive basis for prognosis. There is no doubt that in some cases a diagnosis of the paranoid type would be made by some psychiatrists and of the hebephrenic type by others. In some cases there was a definite cyclic change in the descriptive aspect.

In contrast to the response to shock therapy, there is no significant relation between the results with lobotomy and the duration of mental illness prior to opera-

1. (*a*) Drublin, L.: Further Observations on 62 Lobotomized Psychotic Male Veterans at the Veterans Hospital, Northport, N. Y., J. Nerv. & Ment. Dis. **113**:247, 1951. (*b*) Ramer, P.: Die präpsychotische Persönlichkeit schockresistenter Schizophrener, Schweiz. Arch. Neurol. u. Psychiat. **50**:93, 1942.

2. Rothschild, D., and Kaye, A.: Effects of Prefrontal Lobotomy on the Symptomatology of Schizophrenic Patients, Am. J. Psychiat. **105**:752, 1949.

tion (Table 3). The patients with illnesses of 11 to 15 years' duration showed even better results than the patients with illnesses of 6 to 10 years' duration. A significant decrease in good results is seen only in patients whose disease is of a duration exceeding 20 years.

Neither could we discern from this series a significant relation between age at onset and result of lobotomy. In the discharged group several patients were in their late teens at the onset of their psychosis, and one had symptoms after the age of 40. Similar figures are found for the patients showing no change after lobotomy. Nor does the age at operation seem to be a prognostic criterion (Table 4). At first this was surprising, since early onset of schizophrenia is usually considered typical of resistant forms; but, aside from the fact that our series included very few patients with onset in the early teens, it must be borne in mind that the patients selected for lobotomy are a subgroup of patients with chronic schizophrenia characterized by a

TABLE 3.—*Duration of Psychosis and Result*

	Duration of Psychosis, Yr.				
Result	5 and Less	6-10	11-15	16-20	Above 20
Discharged, %	20	6.6	16	10	6.6
Convalescent care and family care, %	24	13.3	16	10	6.6
Much improved, %	8	13.3	20	20	13.3
Total patients considerably improved, %	52	33.2	52	40	26.5

TABLE 4.—*Result and Average Age at Onset and at Operation*

Result	Average Age at Onset, Yr.	Average Age at Operation, Yr.
Discharged	26.9	35.9
Convalescent care and family care	28	37
Much improved	29.7	41.7
Improved	23.7	40.9
Slightly improved	24.5	37.5
Unchanged and relapsed	28	39

common denominator, namely, behavioristic disturbances, such as destructiveness, violence, and assaultiveness. As emphasized by Freeman and Watts,[3] this emotional component of the psychosis is the outstanding phenomenon on which to base the decision to operate. This factor certainly outweighs all others, such as age and diagnostic type.

The number of male patients as compared with the number of female patients is too small to permit statistical conclusions as to results according to sex. Other investigators [1b] have found that among discharged patients the ratio of males to females was practically identical with that of all lobotomized patients.

Some authors claim a relation between the prognosis of lobotomy and the body type,[4] concluding that if a patient subjected to lobotomy is not a mesomorph, which

3. Freeman, W., and Watts, J. W.: Psychosurgery, Springfield, Ill., Charles C Thomas, Publisher, 1951.

4. Kline, N. S., and Tenney, A. M.: Prognosis in Topectomies and Lobotomies Relative to Body Type, A. M. A. Arch. Neurol. & Psychiat. **65**:323, 1951.

term is practically identical with athletic type, the ratio of a favorable outcome is 1:10. We classified our patients as athletic, asthenic, pyknic, and dysplastic. The number of patients of the last type, is however, too small to be considered. Among the remaining three body types, we could find no differences in results (Table 5).

Table 6 shows the influence of the prepsychotic personality. The patients with inconspicuous prepsychotic personality traits show more favorable percentages than the patients with a schizoid prepsychotic personality. Among the lobotomy-resistant patients the number with schizoid prepsychotic personalities is larger. Table 7 reveals the relation between heredity and prognosis. The lobotomy-resistant patients

TABLE 5.—*Body Type and Result*

Result	Athletic	Asthenic	Pyknic	Dysplastic
Discharged, %	9	20	12.5	16.5
Convalescent care and family care, %	15	10	25	16.5
Much improved, %	21	15	8	33
Total, %	45	45	45.5	66

TABLE 6.—*Prepsychotic Personality and Result*

Result	Normal	Schizoid
Discharged, %	23.1	20.6
Convalescent care and family care, %	13	5.2
Much improved, %	20.4	10.4
Improved, %	28.1	22.4
Slightly improved, %	7.7	13.8
Unchanged, %	7.7	27.6

TABLE 7.—*Heredity and Result*

Result	Heredity Positive for Psychosis
Discharged, %	48
Convalescent care and family care, %	48
Much improved, %	14
Improved, %	25
Slightly improved, %	19
Unchanged, %	56

show a slightly higher percentage with positive heredity than did the discharged patients. It is our impression that the schizophrenic heredity carried a less unfavorable prognosis than did the psychopathic heredity. In many instances the information concerning heredity contained in the records in this series was incomplete.

Bleuler [5] offered a classification of the schizophrenic psychoses based on the type of the course. He distinguishes seven types: (1) acute onset leading to deterioration; (2) gradual onset leading to deterioration; (3) acute onset leading to slight scarring or defect; (4) gradual onset leading to slight defect; (5) undulating course leading

5. Bleuler, M.: Das Wesen der Schizophrenie-Remission nach Schockbehandlung, Ztschr. ges. Neurol. u. Psychiat. **173**:553, 1941. Ramer,[1b] Siegfried, S.: Untersuchungen über Krankheitsverlauf und Familienbild bei schockresistenten Schizophrenen, Schweiz. Arch. Neurol. u. Psychiat. **50**:108, 1942

to deterioration; (6) undulating course leading to defect, and (7) acute onset with spontaneous recovery without scarring. Obviously, Types 3, 4, and 6 are the less malignant and, except in occasional cases of Type 6, will not require lobotomy. Of the lobotomized patients in this series, the majority belongs to Type 5; the second largest, to Type 2, and approximately one-third, to Type 1. As demonstrated in Table 8, Type 5 gives by far the best results, and Type 2 is prognostically considerably less favorable. Fairly good results are obtained with Type 1. So far it seems to us that, except for preservation of emotional response, the type of course of the psychosis gives the most important prognostic clue.

The fact that so-called schizophrenic deterioration of many years' standing can be reversed in a certain number of cases by prefrontal lobotomy indicates that at least in these cases the apparent deterioration was the result of psychotic manifestations masking the still relatively intact mental capacity of the patient. In differentiating such pseudodeterioration from true deterioration before operation, an amobarbital-sodium (sodium-amytal®) interview may give valuable information. Another important and practical prognostic sign is a history of recent temporary favorable response to electric convulsive therapy.

TABLE 8.—*Type of Course of Psychosis and Result*

Result	Type 1	Type 2	Type 5	Type 6
Discharged, %	2-11.5	0	10-20.7	1
Convalescent care and family care, %	2-11.5	4-13	9-18.3	0
Much improved, %	5-28	3-10.1	8-16	0
Improved, %	3-16.5	9-30.4	13-26.8	0
Slightly improved, %	3-16.5	4-13	4-8	0
Unchanged, %	3-16.5	11-33.5	5-10.2	0

Improvement after lobotomy may sometimes be noticed instantaneously after section of the last quadrant. In other cases improvement appears in the manner of a delayed reaction and can be expected to be apparent up to one year after lobotomy.[5] Patients who react with coma followed by psychomotor retardation must usually be allowed considerable time for rehabilitation. If after one year no improvement is evident, further psychosurgery must be considered.

Prefrontal lobotomy has proved to be a very important measure in the treatment of severe chronic mental illness, particularly of schizophrenic and affective disorders.[6] The greatest disadvantage of the standard lobotomy procedure is that it is time-consuming and requires elaborate postoperative care. Since early in 1951 we have used the transorbital approach, which enables us to operate on a far greater number of patients. The future will show whether transorbital lobotomy produces results similar to those of the standard method.

SUMMARY

A series of 122 cases of lobotomy at the Binghamton State Hospital is presented and analyzed. Sixty-four per cent of the total series of patients showed considerable

6. Mettler, F. A., Editor: Selective Partial Ablation of the Frontal Cortex: A Correlative Study of Its Effects on Human Psychotic Subjects, Columbia-Greystone Associates, Problems of the Human Brain, New York, Paul B. Hoeber, Inc., 1949, Vol. 1.

improvement, and 28.5% were able to leave the hospital. The mortality rate was within the limits of international statistics.[7] As to prognostic clues in the schizophrenic group, we found that, aside from the all-important emotional factor, the best are the type of course of the disease, as classified by Bleuler, and the type of response to electric convulsion therapy. The descriptive types, duration of illness, and age did not prove to be of decisive significance. Certain differences could be noticed in connection with prepsychotic personality and heredity. Relobotomy should not be considered prior to one year of postoperative observation.

7. Board of Control (England and Wales): Prefrontal Leucotomy in 1,000 Cases, London, His Majesty's Stationery Office, 1947. Freeman and Watts.[3] Solomon, H. C.: Prefrontal Leucotomy: An Evaluation, J. A. M. A. **140**:1079, 1949.

PAPILLEDEMA

Its Differential Diagnosis, with Special Reference to Minimal Testing of the Blind Spot at Two Meters

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BEFORE describing the fundus conditions simulating papilledema, it is advantageous to discuss the important clinical features of papilledema that will be used as criteria. In using the term "papilledema," we limit ourselves in this paper to the edema of the optic disk due to increased intracranial pressure. The clinical features will be discussed under the following headings: (1) appearance of the fundus; (2) the normal blind spot; (3) histological appearance in papilledema and mode of effect on the blind spot; (4) visual impairment due to papilledema; (5) differences in responses of various optic disks to increased intracranial pressure.

APPEARANCE OF FUNDUS IN PAPILLEDEMA

Typical, well-developed papilledema usually offers no challenge to the trained observer. Bilateral congestion of the optic disks, with obscuration of the disk margins, loss of the physiological cups, and fullness of the veins, together with hemorrhages and exudates confined to the disk and its immediate neighborhood, constitute a typical picture. When only some of these features are present, the problem is more difficult to resolve. For example, we have seen discrete temporal margins, as well as preservation of cupping, despite definite evidence of papilledema. Fulness of veins may often occur in normal persons and may be difficult to evaluate unless a detailed description of the previous normal appearance of the patient's fundi is available. Hemorrhages are often absent with even severe papilledema. As for dioptric elevation of the disk, we place little reliance on it alone, either as a sign of the presence of papilledema or as an index of an increase or a decrease in its extent. Actually, some disks without any papilledema may show a good deal of elevation, while others, with severe papilledema, may not show much. This discrepancy will be explained later in the presentation of the pathological picture in papilledema. As for laterality, with true papilledema, due to increased intracranial pressure, we have never seen complete unilaterality which lasted more than a day or two. When papilledema remains completely unilateral, with an apparently normal disk in the other eye for more than a few days (and this statement assumes that minimal testing of the blind spot of the apparently normal eye shows no enlargement), one should look for a local lesion, such as occlusion of the central retinal vein, optic neuritis, or local orbital or orbito-apical disease causing unilateral papilledema.

Read at a meeting of the New York Society of Neurosurgery, Oct. 16, 1951
From the Neurosurgical and Ophthalmological Services of the Mount Sinai Hospital.

THE NORMAL BLIND SPOT

The normal blind spot owes its existence to the absence of the neuroepithelial layers (rod and cone, and nuclear) in the posterior portion of the retina, where the confluent nerve fibers from the entire retina run together and leave the globe through the choroidal foramen and openings in the sclera called the lamina cribrosa, to continue in the orbit as the optic nerve. This blind spot, or area caeca, lies in the zone between 13 and 18.5 degrees temporal to the point of fixation, thus measuring 5.5 degrees in width. Its length is 7.5 degrees. Fortunately for our function-testing technique, this area is constant enough in size to be of important clinical significance, especially when large test objects, such as 5 or 10 mm. white, are used at a distance of 2 meters. Actually, there is an additional zone of 1 degree around the normal blind spot where the rods and cones which are present are not quite as sensitive as the rods and cones beyond this 1-degree zone. This 1-degree pericecal zone is partially amblyopic in most persons and may be detected by using a small test object, such as 2 mm. white, at 2 meters. Therefore, a normal blind spot that has this 1-degree pericecal zone of partial amblyopia for 2/2000 white would measure an additional 1 degree more in all meridians. In other words, while a blind spot may normally measure 5.5 degrees in width by 7.5 degrees in length for 2/2000 white, in most persons it will be longer and will show as much as a 1-degree pericecal zone of partial amblyopia, and thus may normally measure up to 7.5 degrees in width and 9.5 degrees in length. It is apparent from the above discussion that minimal changes in the blind spot should, and do, show up when 2/2000 white is used. With this test, if a blind spot is no larger than 5.5 by 7.5 degrees, one is safe in saying that there is no evidence of papilledema. On the other hand, if the blind spot is up to 7.5 degrees in width and 9.5 degrees in length, thus falling into the pericecal zone of partial amblyopia, it is likely to be normal for the great majority of subjects and cannot be considered enlarged unless that patient's blind spot had been measured by the same technique in the past and found to be less than this size.

At this point, we shall describe in detail the technique we use in measuring the blind spot. For minimal testing, and this should be routine unless frank papilledema is present, we use a 2 mm. white spherical test object at 2 meters under 10 to 12 f. c. of light. The patient, wearing his distance correction, is made comfortable with a chin rest. After the blind spot has been located, the test object is moved slowly from the nonseeing to the seeing area. As one approaches the limits of the normal blind spot, the test object should move no faster than ⅓ or ¼ degree per second. The motion must be a steady linear one, without any zigzag side movements. The nasal and lateral borders are outlined first, about 1 degree below the horizontal meridian, at a point corresponding to the vertical middle of the blind spot, the movement being steady and at right angles to the nasal and temporal borders. Dull black pins are inserted at the medial and lateral borders thus found. After this, the upper and lower borders are similarly determined. However, at the upper and lower borders the presence of angioscotomas must be considered. To this end, when the upper border of the blind spot is reached, the test object is moved transversely across its very edge, for example, from nasal to temporal side, with the same speed as that mentioned above (Fig. 4). If the test object has not been seen, it is raised another 0.25 degree and swept across from the temporal to the nasal side, still parallel to the upper border, until the nasal side is

reached again. This technique is continued until the test object is first visualized, even if it is for only an instant, because this is the point which represents the seeing retina in the angle of the V which is formed by two adjacent angioscotomas. A black pin is inserted at this point, and the lower border is identified in the same way.

Between the four pins indicating the vertical and lateral borders, four more readings are made, thus giving a total of eight points in the outline of the blind spot. Special care should be taken in the region of the lower temporal border, where the visual perception is often very poor. In this area, slow, careful testing must be done so as to avoid outlining an erroneously enlarged lower temporal border. Once these eight pins are inserted, the height and width are measured in degrees with the tangent rule, which is a wooden stick marked off in tangent degrees. These measurements need not be made at exactly the vertical and horizontal axes, but, rather, should be made in the longest and widest meridians. In other words, the blind spot may be askew because of some anatomical variation or because of some rotary element of the globe during fixation. For the same reasons, a blind spot may be so peculiarly located that its greatest area does not coincide with the usual position of the normal blind spot. Such malposition is of no clinical significance, and the vertical and horizontal measurements of the blind spot are made without regard to its position.

In use of the tangent rule, the zero-degree end of the rule shall coincide with the vertical meridian on the screen, permitting measurement of the width of the blind spot in degrees. In measuring its height with this rule, it is best to lay the rule along the longest axis of the blind spot, even if this line is askew, the 15-degree point being kept somewhere near the middle of this axis and the height being read off in degrees. Blind spots larger than 7.5 by 9.5 degrees with 2/2000 white should be considered abnormal. With a test object as large as 5/2000 white, any enlargement over 5.5 by 7.5 minutes may be considered abnormal. These statements apply, of course, to disks which show no ophthalmoscopic evidence of any peripapillary change, such as a scleral crescent or medullated fibers.

While there has been difference of opinion on the next point, we can say with confidence that we have never seen papilledema with a completely normal blind spot provided the blind spot is plotted with a minimal test object, such as 2 mm. white at 2 meters. On the other hand, we have found the blind spot enlarged before ophthalmoscopic evidence of papilledema was apparent.

HISTOLOGICAL APPEARANCE OF RETINA IN PAPILLEDEMA

While there is a good deal of controversy as to how increased intracranial pressure is transmitted to the nerve head, there is no doubt that edema does exist in the nerve head. This edematous tissue presses upon the peripapillary percipient elements and their nuclear layers, displacing them centrifugally and compressing them at the same time (Fig. 1). The displacement causes an absolute enlargement of the blind spot, while the additional compression of the rods and cones probably accounts for the even greater enlargement shown with the use of smaller objects, such as 3/2000 or 2/2000 white. It is obvious that a highly increased intracranial pressure may cause much displacement and compression of the retinal neuroepithelium without much visible elevation of the disk.[1] Moreover, dioptric measure-

1. Samuels, B.: Histopathology of Papilledema, Tr. Ophth. Soc. U. Kingdom (Pt. 2, 1937) **57**:529-556, 1938.

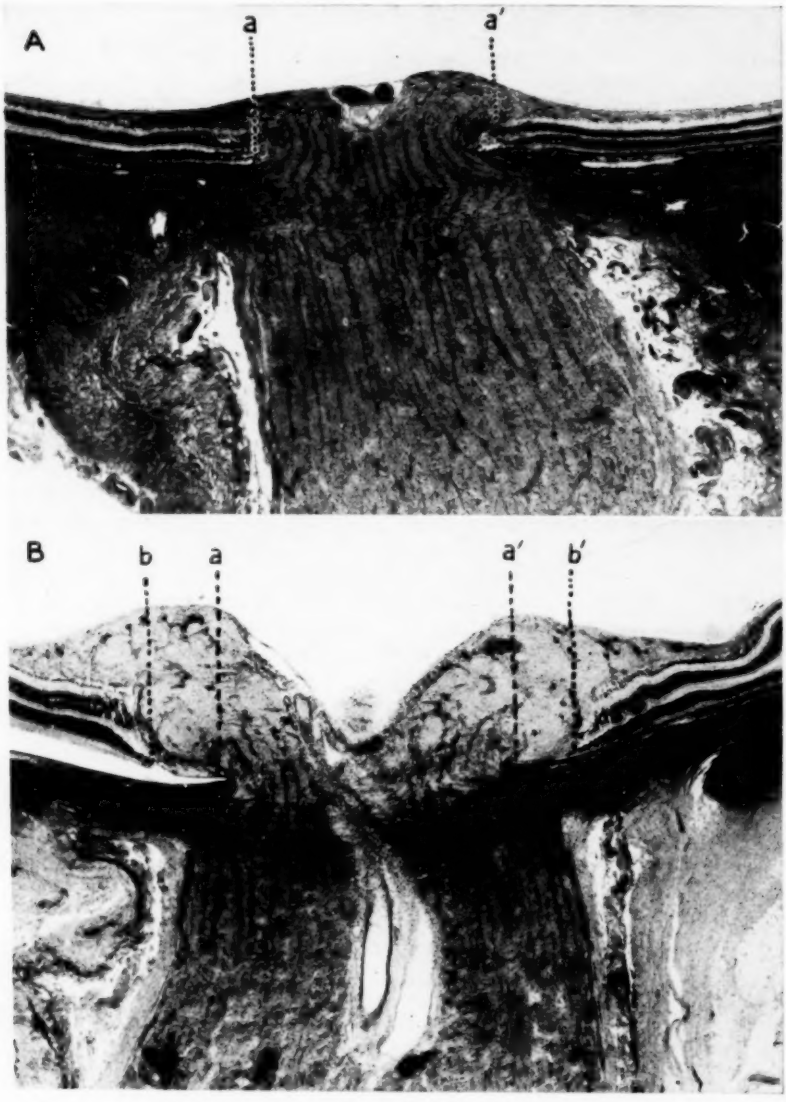

Fig. 1.—*A*, horizontal section of the posterior segment of the normal eye, showing relation of retinal percipient elements and nuclear layers to the optic nerve. Points of termination of retinal nuclear layers at diametrically opposite sides of the optic nerve are represented by *a* and *a′*. The distance between these points represents the area caeca, or normal blind spot.

B, horizontal section of the posterior segment of an eye that shows the typical displacing and compressing type of papilledema, photographed to the same scale as *A*. Points where termination of retinal percipient elements and nuclear layers should be expected normally are represented by *a* and *a′*. The distance between these points may actually have been less in this specimen. The points to which these retinal elements have been diplaced by the edema in the swollen nerve head are represented by *b* and *b′*. The distance between these points represents the width of the enlarged blind spot.

ment of elevation of the disk often presents technical difficulties, especially to observers whose accommodation is not easily relaxed. Hence, we have found the exact tangent-rule measurement of the blind spot to be a much more sensitive and accurate criterion of the amount of papilledema than is the estimation of the dioptric elevation of the disk. Similar conclusions were reached in 1929 by Davis,[2] who found the size of the blind spot a better guide to the degree of papilledema than the dioptric elevation of the disk.

In all field studies it is obviously important to measure the blind spots carefully in terms of actual degrees. Here, transposition of the elicited points from this screen to the visual field charts, without measurement with a tangent rule, can be so inaccurate as to be unreliable for comparative studies on follow-up visits. Such follow-up-studies may reveal a widening of the blind spots as the first significant clinical sign of increased intracranial pressure in cases of questionable papilledema in which the neurosurgeon had not found enough indication for air studies, or even lumbar puncture. An example of this is the case of L. F. (Fig. 2), a man aged 38 with a history of vague headache. His disks were hyperemic and showed little or no cupping. The disks could be labeled as only as "suspicious." Photographs of the fundi were taken and the blind spots plotted. Six weeks later, the fundi and clinical symptoms were unchanged, but the blind spot in the right eye showed definite widening, from 7.75 to 8.75 degrees. It was not until about three weeks after the finding of this enlargement that convincing ophthalmoscopic evidence of papilledema was first noted in the disks. An acoustic nerve tumor was subsequently removed successfully.

Slight variations, up to 0.5 degree or so, may be equivocal, but a full degree on the 2-meter screen in the pericecal area, corresponding to about 3.7 cm., or 1½ in., is a very significant distance. This is especially true when it is the width of the blind spot that is affected, as in this case. An increase in its height is less significant, and this measurement may be more inconstant than the width because of the angioscotomas coming off from the upper and lower borders of the blind spot.

To the examiner who takes the responsibility of observing a patient suspected of brain tumor for the presence of early papilledema, the exact plotting of these blind spots with minimal test objects is of prime importance. At the same time, detailed notes should be made of each disk as to margins, color, cupping, and vessels. For example, if the record shows that the entire margin of the patient's left disk was discrete and that subsequently the nasal portion showed definite blurring, one may well say that an active process, such as papilledema, is present. In addition to descriptive notes and measurements of the blind spot, one should obtain, whenever possible, pictures of the fundus, which may show details that defy mere verbal description.

VISUAL IMPAIRMENT DUE TO PAPILLEDEMA

Loss of visual field from papilledema comes about in two ways: (1) pericecal spread of the enlarged blind spot, with ultimate involvement of even the fixation point, and hence of visual acuity, and (2) peripheral contraction, causing increasing encroachment upon the center of the visual field, ultimately reaching the fixation point, to cause loss of central visual acuity. Hence, the loss may be from within

2. Davis, L.: The Blind Spots in Patients with Intracranial Tumors, J. A. M. A. **92**:794-798 (March 9) 1929.

out or from without in. Depending on the duration and the severity of the papilledema, there is a certain amount of reversibility. We have seen improvement in visual fields and in visual acuity continue for as long as one year after intracranial surgery. Once full-blown papilledema has developed and has persisted for some time, the blind spots do not, as a rule, return to completely normal size, although they may become smaller after decompression.

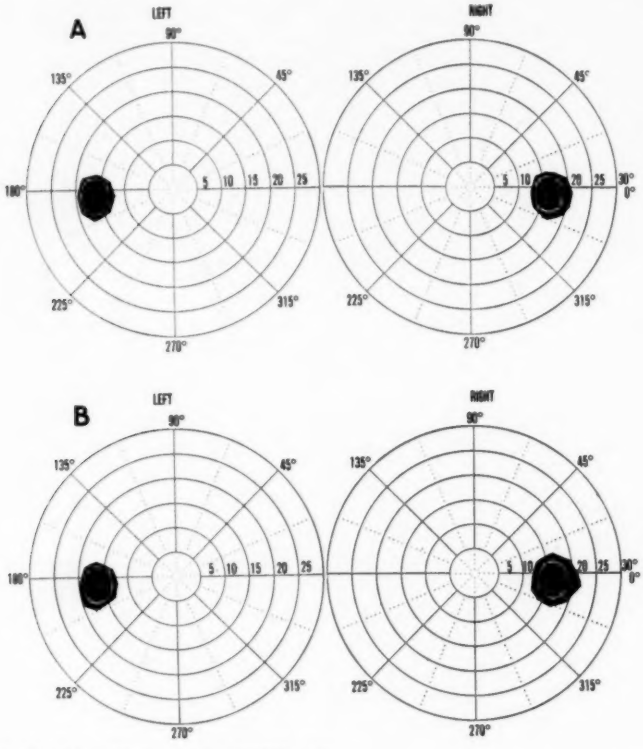

Fig. 2 (L. F.).—Blind spots for 2/2000 white.

A (July 6, 1950), blind spot measuring 7.75 by 9 degrees in the right eye and 7.25 by 8.5 degrees in the left eye.

B (Aug. 29), blind spot measuring 8.75 by 9.75 degrees in the right eye and 7.75 by 8.75 degrees in the left eye.

The very significant change is in the 1-degree increase in the width of the blind spot in the right eye.

DIFFERENCE IN RESPONSES OF VARIOUS OPTIC DISKS TO INCREASED INTRACRANIAL PRESSURE

All clinicians have seen full-blown papilledema in patients in whom clinical evidence of increased intracranial pressure is otherwise minimal, while other patients, with multiple signs of increased intracranial pressure, may show little or

no papilledema. Although we are not yet prepared to give the exact reason for such variations, we believe that the explanation lies in the anatomical and physiological variations of the individual patient. These variations may depend upon (1) the different types of venous drainage from the eye; (2) the intrinsic structure of the sclera; (3) the variation in shape, size, and position of the lamina cribrosa; (4) the size and depth of the physiological cup, and (5) the points of emergence and entry of the central retinal vessels in relation to the optic nerve. The relationship of intraocular pressure to fluid exchange in a particular eye may also play a role. These considerations are purely theoretical and have yet to be studied. Nevertheless, whatever the reason, we do know that in different persons the same amount of increased intracranial pressure will result in great dissimilarity in the degree of papilledema.

DIFFERENTIAL DIAGNOSIS

In discussing the differential diagnosis of papilledema, we shall consider nine conditions, all of which fall under three heads: (1) congenital and developmental, (2) inflammatory, and (3) vascular.

I. Congenital and developmental
   1. *Pseudopapilledema (pseudoneuritis)*
   2. *Hyaline bodies*
   3. Myopic changes around disk
   4. Medullated nerve fibers

II. Inflammatory
   5. *Optic neuritis*
   6. Chorioretinitis juxtapapillaris

III. Vascular
   7. Hypertensive neuroretinopathy
   8. Vascular sclerosis (peripapillary)
   9. Thrombosis of central retinal vein

Six of these conditions are less frequently encountered as problems in differentiation from papilledema, and these will be discussed first (I:3,4; II:6; III:7,8,9). The other three conditions (italicized in the tabulation), which we have found to occur most frequently as problems in differential diagnosis, will be discussed in greater detail.

Conditions Less Frequently Encountered as Problems in Differentiation from Papilledema.—Myopic Changes Around the Disk: Highly myopic disks often show bizarre structural changes which may be confused with papilledema. The absence of hemorrhages and lack of venous congestion are very helpful. Furthermore, highly myopic disks do not, as a rule, show papilledema as readily as normal ones, even in the presence of increased intracranial pressure. On the other hand, peripapillary changes of myopia will also produce enlargement of the blind spot. However, in myopia, when there is no ophthalmoscopic evidence of peripapillary change, such as a scleral crescent or posterior staphyloma, the blind spot should be completely normal. Therefore, if a myopic patient having no myopic changes in the retina or choroid around the disk presents an enlarged blind spot, he must be suspected of having papilledema, as any nonmyopic person.

Medullated Nerve Fibers: Normally, medullation of the optic nerve fibers stops just behind the lamina cribrosa. In some cases it extends beyond the lamina cribrosa, and one sees a developmental anomaly consisting of medullation of nerve

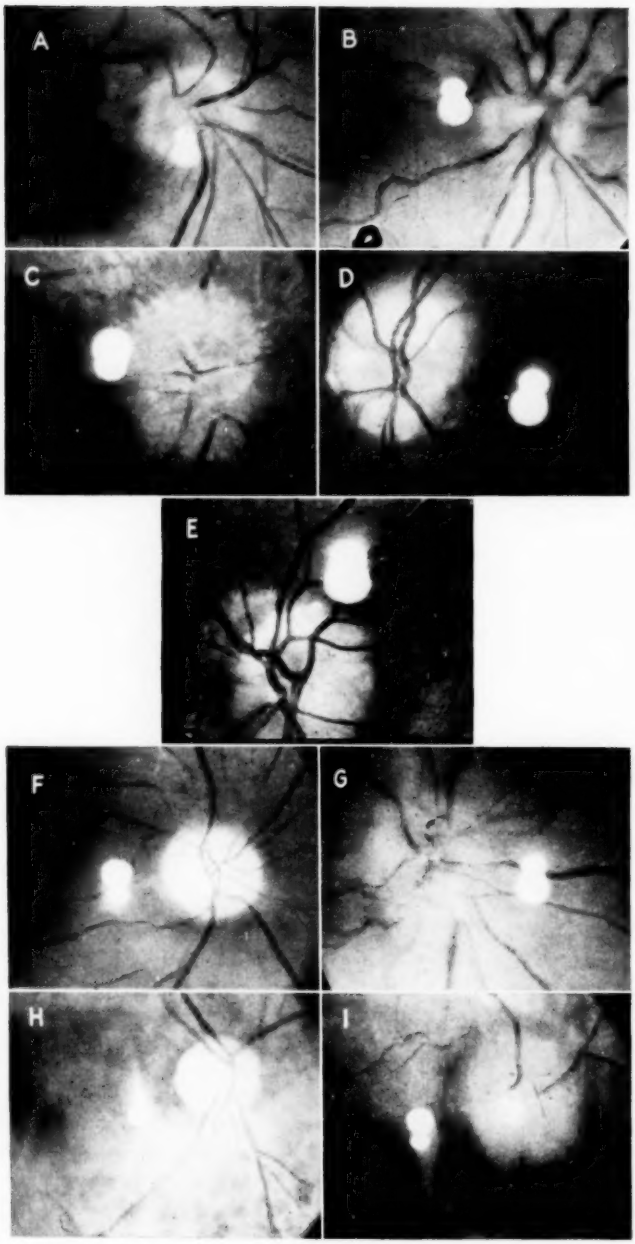

Figure 3

fibers in the retina. These fibers usually occur around the disk as whitish, brush-like striations coming off from the upper and lower margins of the disk and cause an enlargement of the blind spot. They have no clinical significance, except for the possible confusion with papilledema or other disease of the fundus. In older persons, they are usually not so white and do not end in such sharp, feathery lines as in younger persons, but become yellower and duller, the striations being less apparent. It is in such cases that the anomaly is more likely to resemble edema of the nerve head. Incidentally, we have had occasion to see the gradual disappearance of medullated fibers in patients in whom postneuritic atrophy developed.

Chorioretinitis Juxtapapillaris (Jensen's disease) : This condition is an inflammation of the choroid and retina very close to the disk, and the proximity to the disk may be such as to give the appearance of papilledema. Actually, this disease usually occurs in one eye at a time. Furthermore, a dark area usually appears in time, owing to migration of the pigment from the pigment epithelium, as in any type of chorioretinitis in other parts of the fundus (Fig. 3*A*). The field changes consist either in an enlarged blind spot or a cecocentral scotoma, depending on the position of the affected area in relation to the disk, or, not very frequently, in a nerve-fiber-bundle defect, these changes sharply differentiating this disease from the mere enlargement of the blind spot of papilledema.

EXPLANATION OF FIGURE 3

Fig. 3.— *A*, peripapillary chorioretinitis. At the onset, the appearance of the fundus was very suggestive of papilledema. At the time this photograph of the fundus was taken a dark area of pigment began to show.

B, pseudopapilledema. Right fundus of a young woman complaining of headaches. The disks looked alike and showed much blurring and some elevation, but no hemorrhages. However, measurement of the blind spot of the disk in the right eye with 2/2000 white fell within the 1-degree pericecal zone. Technically, it is possible that the patient's normal blind spot was only 5.5 by 7.5 degrees and that the present measurements of 7.5 by 9.5 degrees represented enlargement. However, experience has taught us that true papilledema presenting such a picture would cause more than the 1-degree enlargement that we found. Therefore, a diagnosis of pseudopapilledema was made, and the patient was not subjected to air studies or angiography. Reexamination one year later showed no appreciable change in the fundi or in the size of the blind spots. The headaches had disappeared spontaneously.

C, amorphous hyaline tissue. Right fundus of a young woman who had no complaints except for visual disturbances due to a refractive error. On routine ophthalmologic examination, both disks showed a great deal of yellowish amorphous tissue, causing much blurring, with loss of the physiological cup, but no hemorrhages. The blind spots for 2/2000 white measured 11 by 14.5 degrees in the right eye and 9 by 11.75 degrees in the left eye. With 5/2000 white, the measurements were practically the same. The patient had no other signs or symptoms suggestive of increased intracranial pressure, and the visual fields showed no significant contractions, while the enlarged blind spots showed no threat of encroaching on the fixation point. Photographs of the fundus were therefore made, and no further work-up was done at that time. Reexamination one month later showed no changes in the fundi as compared with their appearance in the original photographs, and the measurements of the blind spots showed no appreciable changes.

D, drüsen of the optic nerve head. Left fundus of a young woman who complained of headache. The disks appeared swollen, and no cupping was present. Many rounded excrescences were seen projecting from the hazy, yellowish disk. Follow-up study two years later showed no evidence of increased intracranial pressure.

E, drüsen of the optic nerve head. Left fundus of a young woman who complained of headache and presented much blurring of the disks. This fundus shows an excrescence from the disk near the site of the light reflex, as well as suggestions of others along the upper border. The other fundus, however, showed no such excrescences, but a great deal of blurring. Complete investigation, including roentgenograms of the skull, spinal puncture, electroencephalography, and pneumoencephalography, showed no abnormalities.

F and *G*, postneuritic atrophy in the right eye (*F*) and acute optic neuritis in the left eye (*G*) of M. N., simulating the Foster Kennedy syndrome.

H, right eye, and *I*, left eye, in a case of unilateral swelling of the optic disk.

Hypertensive Neuroretinopathy: This condition may well present a challenge in clinical differentiation from papilledema due to increased intracranial pressure. Here, the disks may show congestion, edema, hemorrhage, and exudates. One should make a special effort to get a good view of the periphery of the retina. If one finds hemorrhages or small exudates well away from the disk, as much as 4 or 5 disk diameters, it is very likely that one is dealing with vascular disease. If the arteries well away from the disk also show considerable sclerosis and arteriovenous compression, these signs are additional data favoring the diagnosis of vascular disease. Exudates well separated from the disk, called "discrete" exudates, are more likely to be found in vascular disease, whereas in papilledema due to increased intracranial pressure they are more likely to be near or on the disk. Other evi-

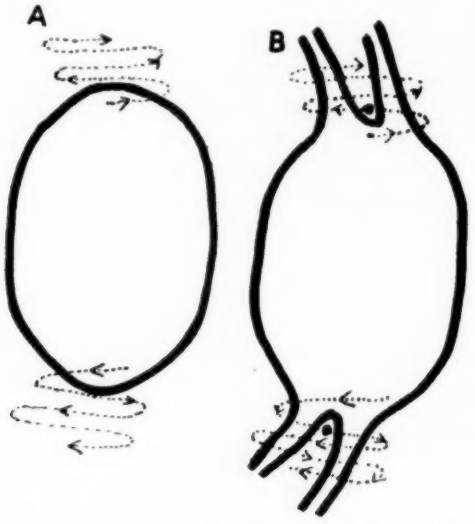

Fig. 4.—*A*, diagram showing direction of movement of the test object in relation to the blind spot on the screen. The direction is at right angles to the angioscotomas. This technique allows measurement of the true length of the blind spot, without the misleading addition of angioscotomas.

B, diagram showing how this technique enables the patient to visualize the test object between the angioscotomas. The heavy dots between the angioscotomas above and below indicate the two points that would determine the shortest, and therefore the true, length of the blind spot in this case.

dence of cardiovasculorenal disease may be helpful. Visual field changes may be similar in both conditions and therefore are not always helpful in differentiating the two conditions.

Greater confusion arises when an intracerebral hemorrhage occurs and acts as an expanding mass in patients with vascular changes in the retina. Furthermore, brain tumors associated with hypertension are also encountered. Such conditions may cause a great deal of difficulty in evaluation of the fundi, and other diagnostic means must be relied on.

Vascular Sclerosis of the Retina: The changes around the disks associated with this condition may be confusing. Often the patient shows enlarged blind spots and small peripheral fields, the picture simulating that of papilledema. However, there is usually no congestion, but a yellowish haze is present around the disk, and the sclerosis of the peripheral retinal vessels in an older patient helps one in making the diagnosis.

Thrombosis of the Central Retinal Vein: This lesion is almost always unilateral. The disk itself usually shows a great deal of swelling, hemorrhage, and exudate. However, the hemorrhages are very large and numerous and extend along the entire venous tree to the periphery of the fundus, involving not only some of the veins, as in hypertensive neuroretinopathy, but practically all of them. Occasionally, in less severe cases, the peripheral hemorrhages are scant and may escape detection unless specifically looked for. Maximum pupillary dilation is necessary in such cases, and the finding of small perivenous hemorrhages far out in the periphery enables one to make the diagnosis.

Conditions More Frequently Encountered as a Problem in Differentiation from Papilledema.—Pseudopapilledema (pseudoneuritis): This name is given to a congenital condition in which the disks appear swollen, and may actually be elevated several diopters, but do not harbor any edema or any tissue that disturbs the retinal neuroepithelium. It occurs often in hypermetropia. While most observers use the term "pseudoneuritis" to describe such a fundi, we prefer the term "pseudopapilledema" because we have found that in most such fundi the condition resembles papilledema more than optic neuritis. For the sake of simplicity, we shall use the term "pseudopapilledema" only. Usually, there is no cup, and all the margins are blurred. The veins may be full and tortuous, although they form large graceful curves rather than the small, acute curves of papilledema. There are never hemorrhages or exudates, and the blind spot is normal. The normal size of the blind spot in pseudopapilledema was well described by Lambert and Weiss.[3]

However, for correct minimal measurements, certain variations of the normal must be recognized. Thus, if the blind spot for 2/2000 white is no larger than 5.5 by 7.5 degrees, one may safely say that the disk shows pseudopapilledema. Even when the 1-degree pericecal zone of partial amblyopia is present, one may call the blind spot compatible with the normal unless the patient was known to have had smaller measurements in the past. As already noted, we have found that most disks show blind spots for 2/2000 white which are much closer to 7.5 by 9.5 than to 5.5 by 7.5 degrees. As a matter of fact, if much "edema" seems to be present and the blind spot is only 7.5 by 9.5 degrees, the size would be a point against the presence of true papilledema, because with true papilledema the blind spot is usually much larger than the 1-degree zone when measured with 2/2000 white (Fig. 3*B*). In evaluating such disks, one should not hesitate to call on other physicians who may have seen the patient a year or two before, when, in the absence of any symptoms, the physician may have had no hesitation about making the diagnosis of pseudopapilledema. Such a record of blurred disks by a colleague can be very helpful. In all such cases, one should make careful measurement of the blind spots and should have the fundi photographed for future comparisons. If the patient

3. Lambert, R. K., and Weiss, H: Optic Pseudoneuritis and Pseudopopilledema, Arch. Neurol. & Psychiat. **30**:580-591 (Sept.) 1933.

continues to complain a month, or even a year, later, the neurosurgeon may find it difficult to reconcile the angry-looking disk with normal intracranial pressure, despite the absence of any other convincing sign of increased intracranial pressure. However, when supported by a photograph of the fundus and blind-spot measurements exactly the same as those made one year previously, the diagnosis of pseudopapilledema becomes reasonable. To summarize, it can be stated that one of our greatest aids in making the diagnosis of pseudopapilledema is the assurance of the size of the blind spot; and the greater the apparent blurring, the more indicative of the absence of increased intracranial pressure is the normal-sized blind spot.

Hyaline Bodies, or Drüsen, of the Optic Nerve Head: This fundus picture is a developmental anomaly in which a whitish or yellowish tissue, believed by some observers to be hyalin, accumulates in the optic nerve heads anterior to the lamina cribrosa. It has also been described as occurring with various types of ocular disease. The tissue may be amorphous and cause swelling of the disk with blurring of its margins (Fig. 3*C*), and it may actually cause the rods and cones to be pushed aside, as in papilledema, thus producing an enlargement of the blind spot. A picture such as this may be very confusing and difficult to differentiate from papilledema, although hemorrhages are never seen in this condition. In many cases the yellowish hyaline tissue may form rounded, refractile coin-like excrescences, called drüsen (Fig. 3*D* and *E*). When even a single one, or the rounded edge of one, is seen in such a disk, the diagnosis of hyaline tissue may be made with reasonable certainty. However, when there are no discrete, coin-like bodies on the disk, or, especially, when all the yellowish amorphous material is buried deep below the surface of the disk, the appearance may resemble that of papilledema very closely. The enlarged blind spot makes matters only more difficult. Again, one should not hesitate to communicate with any colleague who may have seen the patient some time before and have recorded such findings then, thus helping to exclude papilledema. In a series of 9 cases reported by us,[4] as well as about 20 other cases seen by us since, there were some peripheral contractions, mostly nasal and below, but surely not typical enough to permit differentiation from the field changes of papilledema. The work referred to [4] did not demonstrate any central-field defects due to this hyaline tissue. However, other reports did.[5]

It is extremely important, therefore, to search very carefully for such hyaline tissue, and especially for the rounded, coin-like drüsen. The finding of one of these bodies in either eye in the absence of hemorrhages is usually enough to justify the diagnosis of hyaline tissue. In recent years, our experiences with this entity have resulted in our avoiding the use of pneumoencephalography in a large number of cases in which formerly such studies would have been carried out.

We would emphasize again the importance of keeping a record of all examinations of the fundus. One need not go into detail, but may merely indicate the condition of the margins, color, cup, and vessels. Fifteen or 20 well-chosen descriptive words may go a long way in helping a colleague or oneself, at a later date, to make a

4. Chamlin, M., and Davidoff, L. M.: Drusen of Optic Nerve Simulating Papilledema, J. Neurosurg. **7**:70-78 (Jan.) 1950.

5. Rucker, C. W.: Defects in Visual Fields Produced by Hyaline Bodies in the Optic Disks, Arch. Ophth. **32**:56-59 (July) 1944. Chalmers, J. W., and Walsh, F. B.: Hyaline Bodies in the Optic Discs, Brain **74**:95-108 (Oct.) 1951.

diagnosis of pseudoneuritis, drüsen, or true papilledema. True papilledema is not likely to go on for many years without a major episode. Should it do so, neovascularization or secondary optic nerve atrophy, or both, would set in, conditions which do not occur in pseudoneuritis and probably develop very slightly, if at all, in drüsen.

Optic Neuritis: Almost every ophthalmological textbook has a paragraph dealing with the funduscopic difference between optic neuritis and papilledema. While

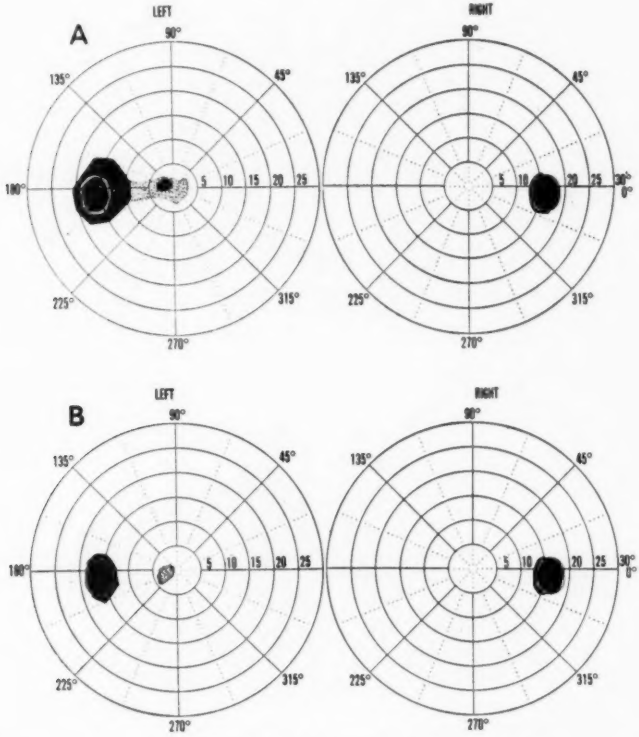

Fig. 5.—*A*, typical cecocentral scotoma in a case of optic neuritis in a young man with a history of sudden onset of blurring in the left eye. Vision was 15/15 in the right eye and 5/100 in the left eye. Central fields are for 5/2000 white. The left disk showed swelling, with hemorrhages, exudates, and blurring of all margins.

B, fields four weeks later. Vision was 15/15 in the right eye and 15/40 in the left eye.

many good differential points are made, a resolution of the problem, based on study of the fundus alone, may be very difficult. In both conditions there are edema, congestion, blurring of margins, hemorrhages, and exudates. The ophthalmoscopic picture of both can be very confusing, even to the trained eye. However, other, much more reliable means of differentiating the two conditions are available. First, optic neuritis is usually unilateral, whereas papilledema is, as stated before, usually

bilateral. Bilateral simultaneous optic neuritis does occur, but it is rare enough to be a strong differential point. In the past six years we have encountered only two cases of simultaneous bilateral optic neuritis. In one case there was bilateral cecocentral defect with some impairment of visual acuity (case of S. W., not demonstrated). In the other there was bilateral nerve-fiber-bundle defect, with preservation of visual acuity of 20/20 (Fig. 9). In the second case, the bilateral edema of the disk, together with preservation of 20/20 vision, made the diagnosis of

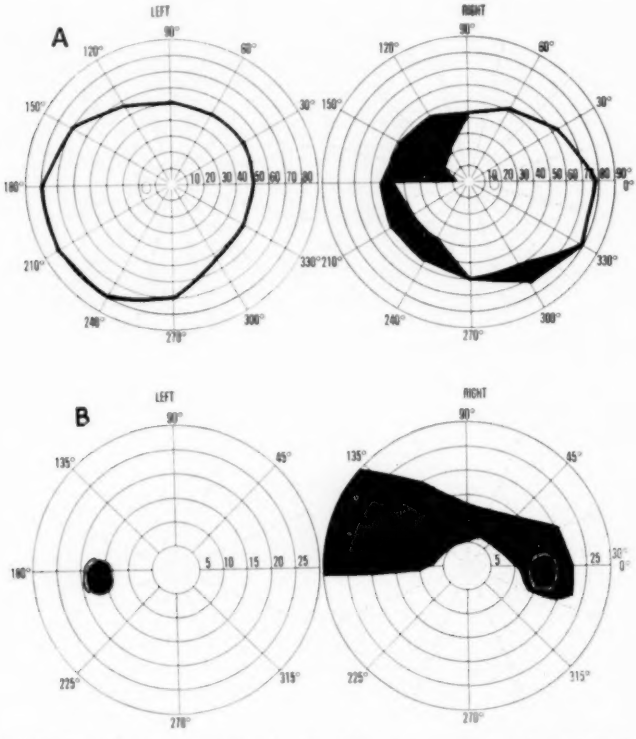

Fig. 6 (K. K.).—Typical nerve-fiber-bundle defect in a case of optic neuritis in a young woman with a history of sudden blurring of vision in the right eye. The right disk showed swelling, blurring of all margins, hemorrhages, and exudates.

A, peripheral field for 3/250 white. Vision was 15/15 in each eye.

B, central fields for 2/1000 white. The central field for 2/1000 white in the right eye showed a nerve-fiber-bundle defect, with resultant nasal defect in the peripheral field. Fixation is spared by 5 degrees, and thus 15/15 vision was preserved in the right eye.

papilledema seem at first a likely one, but, as shown (Fig. 9), the field study established the diagnosis of optic neuritis.

Aside from unilaterality, the differentiation of papilledema and optic neuritis is much more easily recognized from the difference in their effects on the visual field and central visual acuity, a difference dependent on the dissimilarity of the patho-

logical processes. In papilledema there are edema of the nerve head, enlargement of the blind spot, and peripheral contraction. In optic neuritis the pathological process usually consists of an area of infiltration, producing a toxic or necrotizing effect on a particular nerve fiber bundle or on several nerve fiber bundles. The nerve fiber bundle usually attacked is the particularly sensitive maculopapillary bundle, with a resulting cecocentral scotoma. Less frequently, other nerve fibers are affected, causing a paracentral defect or a nerve-fiber-bundle defect. Combinations of the

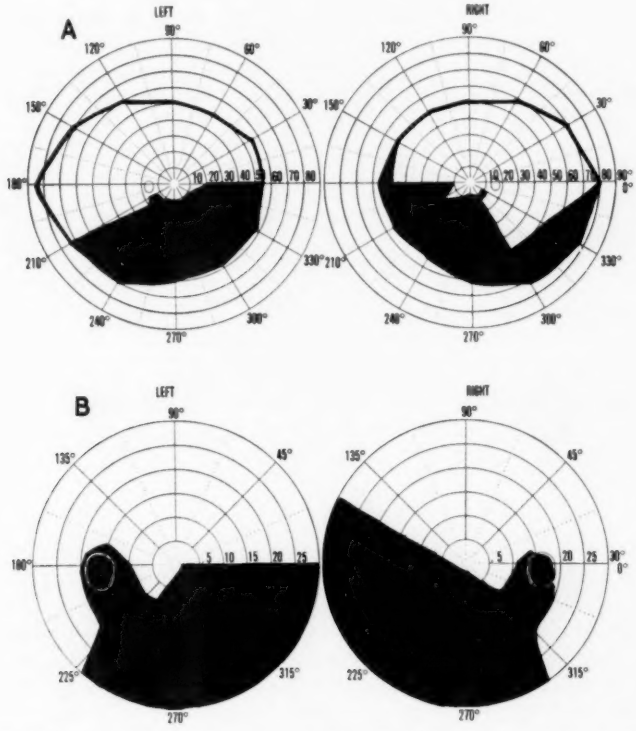

Fig. 7 (M. N.).—Typical bilateral nerve-fiber-bundle defect in optic neuritis in the left eye (Fig. 3 *G*) and postneuritic atrophy in the right eye (Fig. 3 *F*).

B, central fields, showing nerve-fiber-bundle defects for 5/2000 white in the right eye and for 2/2000 white in the left eye. Vision was 20/30 in the right eye and 20/20 in the left eye.

two may occur. Thus, in papilledema the most outstanding change in the visual field is an enlarged blind spot, this enlargement being a defect in the visual field. This defect is densest just around the border of the normal blind spot, but becomes progressively less dense as one leaves the normal blind spot, until it clears. This clearing usually occurs before the defect reaches the fixation point, so that central visual acuity is usually undisturbed. As a rule, if fixation does become involved, a good deal of time elapses before impairment of central vision, which is gradual,

occurs, so that repeated observations can be made. In cases of overwhelming papilledema with rapid loss of central vision, other signs and symptoms of increased intracranial pressure usually make the diagnosis relatively simple. Therefore, in papilledema the patient's complaint of blurring, if any, is usually that of transient, insidious disturbance, accompanied by other symptoms of increased intracranial pressure.

In optic neuritis, on the other hand, the commonest defect is a cecocentral scotoma, involving the point of fixation and thus causing an immediate loss in visual acuity, the onset being rather sudden and the defect reaching its greatest intensity in only a few hours, or in a day or two (Fig. 5). However, not infrequently, instead of a cecocentral scotoma, optic neuritis will produce a nerve-fiber-bundle defect or some other paracentral scotoma, which skirts around the fixation point but does not quite reach it. This will cause a sensation of blurring but will still allow visual acuity of 20/20 and good recognition of color centrally (Fig. 6 and 9). Therefore, it is obvious that one must not rely on 20/20 vision or recognition of a small

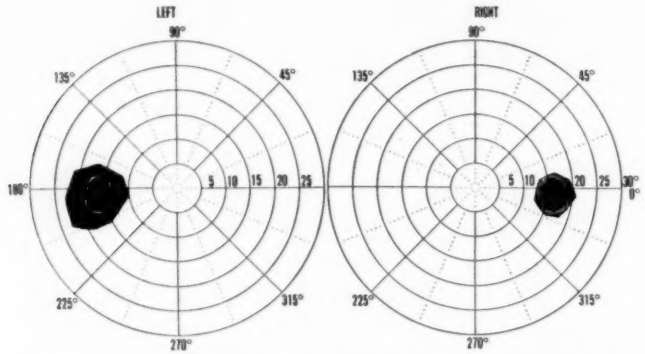

Fig. 8.—Blind spots for 2/2000 white for the fundi shown in Figure 3*H* and *I*.

red test object to rule out optic neuritis, for a nerve-fiber-bundle defect will allow both these phenomena. However, both the cecocentral scotoma and the nerve-fiber-bundle defect are quite different from the enlarged blind spot of papilledema, so that they allow a definitive and thoroughly reliable differential diagnosis on the basis of the field changes alone in almost all cases.

The significance of such field changes is seen in the following case: M. N. presented himself with a history of gradual loss of vision in the left eye. Examination revealed optic nerve atrophy in the right eye and what appeared to be papilledema in the left, thus leading the referring physician to suspect a Foster Kennedy syndrome (Fig. 3*F* and *G*). Central visual acuity was actually good in both eyes. However, visual field studies revealed typical nerve-fiber-bundle defects in both eyes, compatible with optic neuritis, and not with an intracranial mass lesion or increased intracranial pressure (Fig. 7). Subsequent air studies corroborated the absence of any intracranial mass lesion or increased intracranial pressure. Further investigation of the case continued, and eventually a hospital record was found which proved that the blurring of vision in the right eye had occurred suddenly

two years before. In other words, this patient had an episode of optic neuritis in the right eye two years before and our examination showed postneuritic atrophy in that eye, together with acute optic neuritis in the left eye. The field defects were similar in the two eyes and corroborated the diagnosis of optic neuritis.

If the field defect begins to clear spontaneously in a week or two, one has, of course, additional evidence of optic neuritis. Such clearing need not restore central visual acuity but may manifest itself only in a slighter density of the field defect.

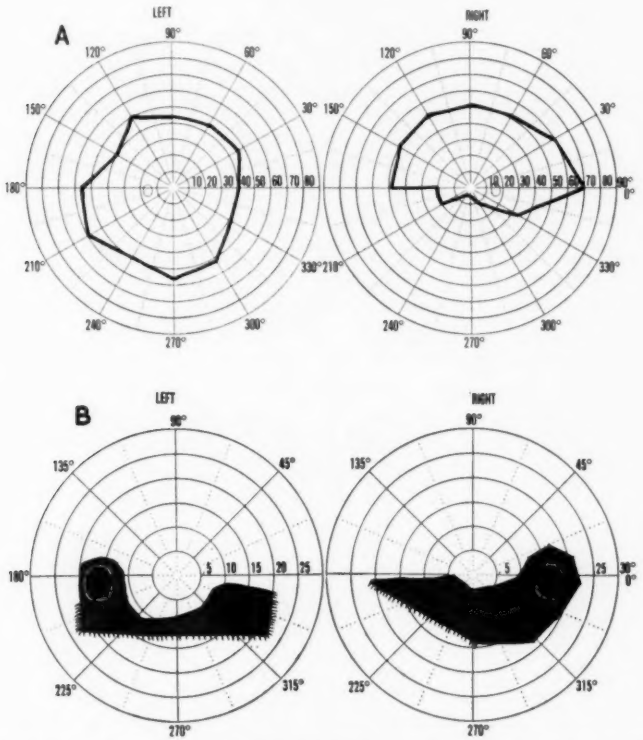

Fig. 9 (T. R.).—Nerve-fiber-bundle defects in bilateral optic neuritis occurring simultaneously in the two eyes. The field defects skirted around the fixation point, and therefore visual acuity of 15/15 was maintained in each eye. The fundi showed edema of the disks with complete blurring of the margins and some hemorrhages.

A, peripheral fields for 2/330 white.

B, central fields, showing nerve-fiber-bundle defects for 2/2000 white. The borders, with small parallel, rib-like lines, indicate the limits to which the scotomas were mapped, not the actual limits.

At this point, we wish to call attention to a case we encountered in which there was sudden onset of bilateral blurring, with visible edema of both nerve heads (Fig. 10). The visual fields showed definite peripheral contraction in the left eye, the defects being very dense and extending centrally, to make the patient aware

of blurring of vision. There was no distinct central, paracentral, or nerve-fiber-bundle defect. Rather, there was a dense peripheral defect in the left eye, encroaching on the central field secondarily. We believe that this case falls into the category of optic perineuritis. Walsh [6] expressed the opinion that such a condition is found in syphilis, as well as in meningitis. In our case there was no evidence of either disease. This condition, because of the absence of a distinct central defect, resembles papilledema very closely. Unfortunately, in some such cases

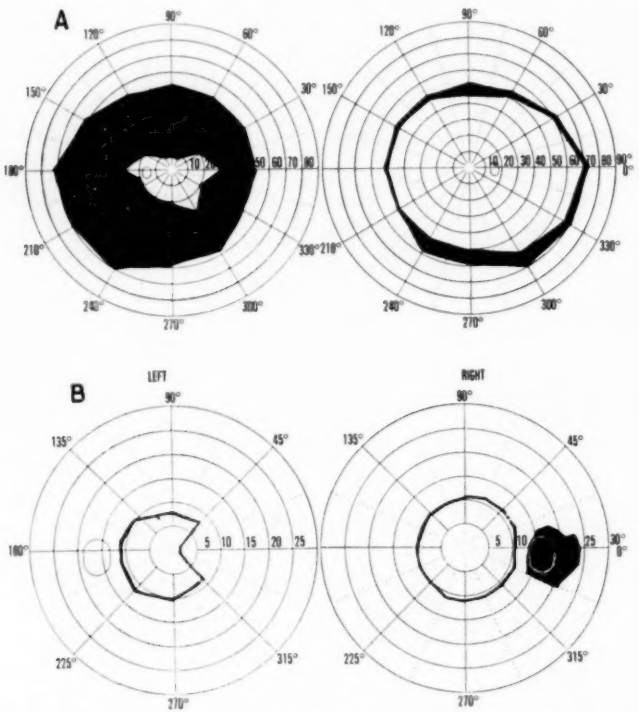

Fig. 10 (H. K.).—Swelling of the disk with complete blurring of margins in a man aged 60, who experienced a sudden loss of vision to his left. Vision was 20/20 in the right eye and 20/40 in the left eye. Lumbar puncture revealed a pressure of 260 mm. of water, 60 mg. of protein per 100 cc. of fluid, and no cells. Burr holes were made, with escape of a considerable subarachnoid fluid, and ventriculograms revealed a normal ventricular system. Subsequent lumbar punctures at intervals of two days revealed normal pressure, with no subsequent rise. The field of the left eye showed marked depression in the periphery, extending centrally. The field of the right eye showed an enlarged blind spot with only a faint peripheral depression, if any. It is our opinion that this case may have been one of optic perineuritis of the left eye, some increase in intracranial pressure causing the edema of the right disk.

A, fields for 2/250 white in the right eye and for 5/250 white in the left eye.

B, blind spot for 5/2000 white and central fields for 1/2000 white (right eye) and for 5/2000 white (left eye).

6. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947, pp. 358-359.

there may even develop an increase in intracranial pressure, thus making the differential diagnosis more difficult. However, the sudden onset, with the predominance of dense peripheral defect, is quite different from the slow, slight loss in the periphery of the field that comes on, as a rule, only after long-standing papilledema.

Finally, the symptom of pain in optic neuritis may be considered. While it is not a constant feature, the patient may complain of pain on motion of the eyeball or of tenderness of the globe when it is pushed back into the orbit. Unilateral pain or tenderness of this sort is a corroborative symptom of an inflammatory lesion in the optic nerve.

In some cases, even though a definite diagnosis cannot be made, a differential from papilledema could be ascertained. For example, *H* and *I* of Figure 3 represent the left and the right fundus of a man aged 52 who complained of headache. The left disk was extremely swollen, so that the margin could not be made out. Despite this, a rather deep, cone-shaped cup could be made out, and hemorrhages were not present. The right disk showed normal color, discrete, clear margins, and a small cup. In addition, there were definite sclerotic changes in some of the more peripheral vessels of the fundus. The left blind spot measured 12.5 by 15 degrees with 2/2000 white, as well as with 3/2000 white. The right blind spot measured 8 by 8.5 degrees with 2/2000 white (Fig. 8). The findings in the rest of the field study were normal. At the time we saw this patient, the marked blurring in the right disk had been observed at least two weeks before. Despite this, the right disk showed no edema whatever, and the blind spot was within normal limits. (The 8-degree width represented only 0.5 degree more than the pericecal zone, but this increase could be attributed to the retinal sclerosis.) While a definite diagnosis could not be made, the persistent unilaterality was convincing evidence that there was no increased intracranial pressure. Roentgenograms of the skull and electroencephalograms showed no abnormalities. The fundi were photographed, and the patient was asked to return in one month, at which time no change in the fundi or blind spots was found. Six months later, again, all findings were unchanged. At the last examination he reported that he was studied at another institution, where lumbar puncture and pneumoencephalograms showed no abnormalities, thus corroborating the absence of increased intracranial pressure.

The unilateral swelling may represent a unique pericecal sclerotic exudate, or even unilateral hyaline tissue, although we have never before seen the latter occur as a completely unilateral phenomenon.

SUMMARY AND CONCLUSIONS

1. The normal blind spot and its variations are described.

2. The pathogenesis of papilledema, as well as the resultant effect on the blind spots, is discussed.

3. A technique for measuring minimal changes in the normal and the abnormal blind spot is presented.

4. A number of fundus conditions that may be confused with papilledema are presented. Of these, the three commonest are pseudopapilledema (or pseudoneuritis), hyaline tissue of the optic disk, and optic neuritis. The differential diagnosis is discussed.

(*a*) Pseudopapilledema is diagnosed largely by the absence of hemorrhages and, most important, by the presence of a normal blind spot.

(*b*) Hyaline tissue in the optic disk may be more difficult to differentiate because the blind spot is enlarged, as in papilledema. Here, one must learn to recognize the appearance of the amorphous yellowish tissue and make a thorough search for any refractile, coin-like concretions.

In case of either pseudopapilledema or hyaline tissue in the optic disk, if the rest of the clinical picture is uncertain and the neurosurgeon does not care to do a lumbar puncture in the face of possible increased intracranial pressure, and if the neurological examination shows no urgent symptoms, photographs of the fundus should be taken and blind spots carefully measured, so that comparisons may be made at reasonable intervals. If loss of vision is the neurosurgeon's concern, safe management consists in frequent measurement of the blind spot and ascertainment of its lack of encroachment on the fixation point. Actually, before central vision is lost in such a mild condition, enlargement of the blind spot goes on for days. Whenever possible, one should communicate with colleagues who have seen the patient several months or years before, for possible help from their records. The importance of the physician's keeping descriptive records of all fundi examined is emphasized. In any event, one must be cautious about diagnosing any condition as papilledema if the fundus does not show hemorrhages and symptoms of increased intracranial pressure are absent.

(*c*) Optic neuritis, with its usual unilaterality, with the reservation indicated above, its sudden onset and its central or paracentral defect, with the characteristic field changes, should as a rule offer no difficulty in differentiation from papilledema.

Despite all the diagnostic criteria, one will still encounter conditions that cannot be differentiated from papilledema by ocular studies alone, and will therefore have to resort to other diagnostic aids, such as pneumoencephalography.

CALORIC STIMULATION IN LOCALIZATION OF BRAIN-STEM LESIONS IN A COMATOSE PATIENT

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NEW YORK

CALORIC stimulation, employing cold water, in the comatose patient results in conjugate tonic deviation of the eyes toward the side stimulated, provided that the vestibulo-ocular brain-stem pathways are intact.[1] The absence of cerebral influence had been held responsible for both the loss of nystagmus and the antagonism to the vestibular impulses. Hence, tonic deviation occurs. If, in addition, the vestibulo-ocular pathway is interrupted in the posterior longitudinal bundle, a fairly definite sequence of events should follow caloric stimulation. The following case report illustrates this predictable sequence.

REPORT OF A CASE

Clinical Abstract.—T. L., a white man aged 47, was admitted to the neurological service of Mount Sinai Hospital on March 31, 1951, because of sudden onset of stupor. He had complained of bifrontal headache and nausea for 24 hours prior to admission. Several hours before admission he suddenly lapsed into stupor. He had not been hypertensive or diabetic. Examination disclosed a well-developed, well-nourished white man who was in a deep stupor. He reacted to painful stimuli by moving all four extremities. There was no evidence of head injury. The neck was supple. The eyes were in midposition. The pupils were constricted and equal and did not react to light. The fundi were normal. A snout reflex was present. Transient symmetrical hyperreflexia and a bilateral extensor plantar response were described, but I found only hyporeflexia, flaccidity, and a neutral plantar response.

Laboratory Data: The cerebrospinal fluid was under an initial pressure of 210 mm. It was slightly xanthochromic and contained 220 crenated red blood cells per cubic millimeter. The total protein was 50 mg. per 100 cc., and Benedict's solution was reduced in five tubes. The white blood cell count was 11,200; the hemogram was normal. Values for the blood urea nitrogen, fasting blood sugar, carbon-dioxide combining power, and chlorides were all normal. The blood bromide level was not elevated. Examination of the urine for barbiturates and lead gave negative results. The serologic test for syphilis and the cerebrospinal fluid complement-fixation test gave negative reactions. The electroencephalogram showed diffuse, symmetrical, slow activity. Roentgenograms of the skull were read as normal.

Caloric stimulation was carried out by injecting 20 cc. of ice water into each external auditory canal with the eyes in the neutral position. After a latent period of 15 to 20 seconds, the ipsilateral eye abducted, while the contralateral eye did not adduct beyond the midline. The eyes remained in this position for one minute, and then the neutral position was resumed. No nystagmus developed. This sequence of events was produced each time the stimulation was carried out.

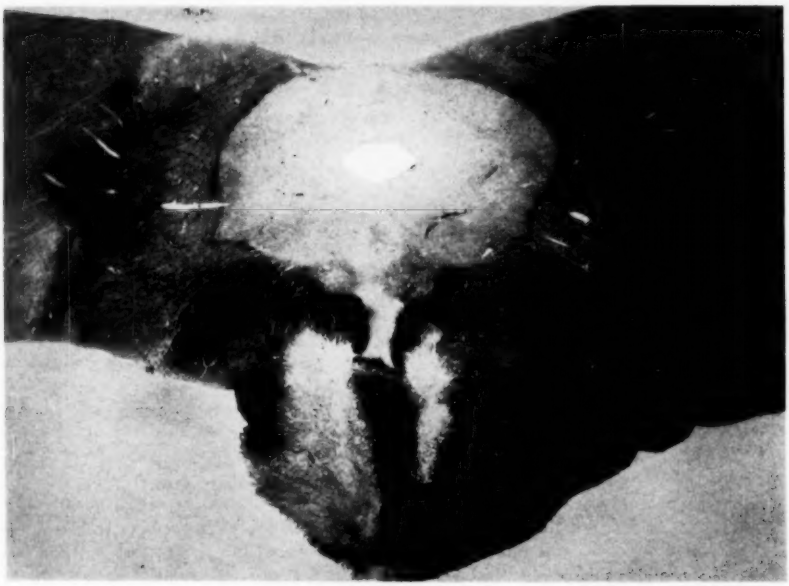
From the Neurological Service, The Mount Sinai Hospital, and the Neuropathological Laboratory, Bellevue Hospital.

1. Merwath, H., and Feiring, E.: Modifications of Induced Nystagmus by Acute Cerebral Lesions, Brooklyn Hosp. J. **1**:99 1939. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 4, St. Louis, C. V. Mosby Company, 1949, p. 4156.

It was thought that the patient had a hemorrhagic and/or thrombotic lesion in the upper part of the brain stem, near the midline, involving the posterior longitudinal bundles.

Course: On the second hospital day the patient became febrile, and signs of bilateral bronchopneumonia developed. Despite intensive chemotherapy, the hyperpyrexic course continued until his death, nine days after admission.

Microscopic Report.[2]—Sections of the midbrain through the inferior colliculus, stained for myelin sheaths, showed a bilateral lesion, with loss of myelin, on either side of the midline, more extensive on one side than on the other, destroying fibers in the decussation of the brachium conjunctivum. The median longitudinal fasciculus was only slightly involved at this level, more on one side than on the other in its anterolateral aspect. The trochlear nucleus shows marked chromatolysis in a considerable number of cells.



Section of the brain stem at the level of the trochlear nuclei, showing bilateral demyelinating lesions which involve the posterior longitudinal bundles at the dorsal aspect of the lesions.

In the upper part of the midbrain there was a larger bilateral, almost symmetrical area of softening on each side of the midline. This involved for the most part the posteromedial aspect of the trochlear nucleus; the tegmentum of the midbrain at this level was missing from the specimen, as cut by the Medical Examiner.

This lesion probably influenced the third nerve nucleus on both sides and possibly some fibers of the third nerve, as well as the decussation of Meynert.

Section of the upper part of the pons showed bilateral degeneration in the pyramidal fibers on both sides of the midline.

2. The Medical Examiner's Office permitted the publication of the pathological material, and Dr. Lewis D. Stevenson provided the microscopic descriptions of the brain sections.

COMMENT

Cold water introduced into the external auditory canal will elicit the vestibulo-ocular response in the comatose patient if the pathway is not interrupted. Normally the impulses responsible for adduction of the contralateral eye in the conjugate gaze mechanism traverse the posterior longitudinal bundle rostrally, from the abducens nucleus to the oculomotor nucleus of the opposite side. The interruption of these impulses results in a characteristic triad. This syndrome has been defined by Spiller [3] and others [4] as paresis of adduction on attempts at conjugate gaze, nystagmus in the horizontal plane, greater in the abducting eye, and nystagmus in the vertical plane. It is known as the syndrome of the posterior longitudinal bundle, or anterior internuclear paralysis. Of this triad of internuclear paralysis, nystagmus, and intact convergence, only the paralysis is demonstrable in the comatose patient. Absence of external strabismus must serve as a substitute for intact convergence.

In the case here presented internuclear paralysis was demonstrated by means of caloric stimulation. This made possible accurate localization of the lesions. Seen in the Figure are two lesions, each involving the ipsilateral posterior longitudinal bundle to some degree, one bundle being relatively more affected than the other. Thus, caloric stimulation provided an additional tool in the localization of brain-stem lesions in a patient suffering severe disturbance in the state of consciousness.

Caution should be exercised in attempting to localize lesions by this method if increased intracranial pressure is present, since, as Madonick [5] has pointed out, the syndrome may be the result of compression of the brain stem by neoplasms of the posterior fossa.

SUMMARY

1. A case is presented in which accurate localization of brain-stem lesions was made possible by caloric stimulation, despite deep stupor.

2. The anatomicophysiological basis for predicting the site of the lesions is discussed.

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4. Bender, M. B., and Weinstein, E.: Effects of Stimulation and Lesion of the Median Longitudinal Fasciculus in the Monkey, Arch. Neurol. & Psychiat. **52**:106, 1944. Cogan, D. C.; Kubik, C. S., and Smith, W. L.: Unilateral Internuclear Ophthalmoplegia, Tr. Am. Neurol. A., 1950.

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HEREDITARY MYOKYMIA

Syndrome or Disease Entity Associated with Hypoglycemia and Disturbed Thyroid Function

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FASCICULAR twitching of voluntary muscles has been described in a number of disease entities, such as the atrophic and dystrophic myopathies, and the toxic, metabolic, and infectious affections of the nervous system, as an associated or a related phenomenon. Explanations have been offered in some instances. Attempts to systematize the problem have been actively in progress for over three decades. Recent able summaries of the subject in its related experimental and clinical ramifications have been highlighted by Rosenblueth,[1] who cited the voluminous studies of the Cannon laboratories, together with much investigation of his own, which point to a stalemate between the chemical and electrical theories of neurotransmission. The authors cited believe that "presynaptic nerve impulses release acetylcholine when they reach the corresponding post-synaptic elements and that acetylcholine elicits characteristic responses." The excellent survey of McEachern and Rabinovitch [2] offers much hope for the more rational attack on clinical disorders of neuromuscular origin. The monumental contributions of Myerhof [3] and of Hill [3] and their laboratories are without equals in the lifetime devotion of these investigators to the fundamental chemical-thermodynamic-physical relations of the nerve-muscle milieu. Immeasurable credit must go to the Szent-Györgyi [4] school for focusing its investigations on the basic constituents of muscle and their responsiveness to the complexities of molecular orientation and electrical, chemical, thermal, enzymatic and ionic shifts.

Observations on undulatory, intermittent muscular fasciculations, accompanied in a few years by the hypothyroid state and by periodic attacks of hypoglycemia and its clinically associated symptoms in one man, and some of the same symptoms in his four sons, have led to the present study. It is intended in this paper to present the case histories, to discuss fasciculations, and to point out features that need

From the Departments of Medicine of Presbyterian Hospital, and the University of Illinois College of Medicine.

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2. McEachern, D., and Rabinovitch, R.: Advances in Neuromuscular Disorders, in Advances in Internal Medicine, edited by W. Dock and I. Snapper, Vol. 4, Chicago, The Year Book Publishers, Inc., 1950, p. 20.

3. Hill, A. V.: A Challenge to Biochemists, in Nachmansohn, D.: Metabolism and Function, Houston, Texas, Elsevier Pub. Co., 1950, p. 4.

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further study for elucidation of the normal and pathological neuromuscular relations in muscle contractions.

REPORT OF CASES

Study of the Father.—A man aged 58, 6 ft. 3 in. (190.5 cm.) in height and 145 lb. (65.8 kg.) in weight, first entered Presbyterian Hospital on Sept. 10, 1940. The principal items in the history follow: 1. He had complained of attacks of fatigability and weakness, of progressive severity, for 25 years. The symptoms were first noted in 1915, after a severe illness with typhoid, while the patient, with his family, was a missionary in Turkey in Asia during the war and massacre. Weakness of the voice, without infection of the respiratory tract, periodically necessitated the cancellation of speaking engagements. He had amebiasis in 1920, but this was not incapacitating. X-ray studies in 1920 revealed healed pulmonary tuberculosis. His attacks of weakness became severer after two bouts of dengue, in 1928. At the time of admission attacks were manifest in periodic exhaustion, which was intensified by the effort of normal defecation, talking, or sustained attention. 2. Epigastric pain and generalized abdominal distress, with low-lumbar backache and sciatica, were studied at Clifton Springs Sanitarium, where in 1930 a cholecystectomy and an appendectomy were done. Exploratory laparotomy and posterior gastrojejunostomy, with the patient under tribromoethenol-ether anesthesia, were accomplished in 1933 for inadequate gastric emptying and adhesions. 3. Fibrillary twitching of muscles, chiefly of the calves, was studied at the Mayo Clinic in 1930, 1932, and 1934. Tonsillectomy was done in 1932. 4. Episodes of postprandial weakness began after the operation in 1933 and became more pronounced in 1938, occurring about two hours after any meal and during the early morning. Attacks started with a sensation of tension in the abdomen and progressed to vertigo with hunger pangs, followed by brief visual scotomas, profuse sweating, numbness of the finger tips, mental fogginess, diminished visual acuity without a field pattern, amnesia, confusion, inability to express ideas, and sleepiness. There were no convulsions. The last five symptoms invariably occurred within one-half hour after cessation of the early symptoms of the episode. No effect on muscular twitching has been observed.

Examination[5] revealed an alert, intelligent man, deliberate in action, who presented a moderate funnel deformity of the chest and slight webbing of the third, fourth, and fifth toes on the right; his voice was weak, and at times tremulous; enunciation was slow and clear.

Fibrillary twitchings were visible under the thin skin of the calves, the posterior and anterior aspects of the thighs, the buttocks, the thenar eminences, the posterior aspect of the forearms, the anterior and posterior aspects of the upper arms, the masseter, temporal, interosseus, intercostal, and rectus abdominis muscles, and the eyelids, lips and tongue. These fibrillations were scattered, being visible perhaps at one place only at a time; in the calves they tended to be undulatory and, when active, to cover a 3- to 10-cm. stretch at a time and then to appear at another point quite distant. There was no apparent rhythm or circuitous routing. The twitchings were not rapid and were easily followed by the eye. They did not result in general muscle shortening. They were not modified by faradic or induced stimulation. Occasionally a cramp in the calf or foot was followed by more active fibrillation. The patient was conscious of the more prominent contractions, but was rarely awakened by them. They occurred with the same intensity and distribution in sleep as when he was awake. They were not increased by mild trauma, such as sharp flexion or extension or a stroke with the percussion hammer but continued unchanged during voluntary flexion of the muscle. Reflexes were all within normal limits and equal. There was no dysesthesia or atrophy. Coordination and muscle tone were normal. No tremor was apparent in the extended fingers.

The abdominal muscles were thin; the panniculus was minimal. Scars were present in the right rectus area and the midline, without herniation. The liver was barely palpable on deep inspiration. The kidneys and spleen were not palpated. No masses were defined, and undue tenderness was not elicited. The ocular fundi were normal. Visual acuity was fluctuating and was temporarily corrected with lenses, much as in the eye of the patient with poorly controlled diabetes. The fields were normal. The physical condition was otherwise normal.

5. Cooperation in examination at the first admission was participated in by Drs. Peter Bassoe, Wilber E. Post, Willard O. Thompson, John Olwin, Milnor Freeland, Edwin Miller, Laurence S. Jennings, William Haines, Ernest E. Irons, Vernon Leech, and Loren Avery.

The hemoglobin meausred 70% (Newcomber); the red blood cell count was 4,150,000, and the white blood cell count, 6,800. Morphologically the cells and thrombocytes were normal. There were no parasites. The hematocrit reading was 39%. The Kahn reaction of the blood was negative. The blood group was O. Roentgenologic examination showed that the kidneys and nearby shadows were within normal limits. There was moderate lipping of the lower thoracic and the lumbar vertebrae. The lungs and heart were normal. The colon was normal. The stomach emptied through both the pylorus and the enterostomy stoma. No deformity was seen. The sella turica and skull appeared normal. The electrocardiogram was within normal limits; no adventitious currents were registered. The vital capacity of the lungs was 3,000 cc., which is 63 to 69% of normal for the patient's surface area, height, and weight. Values for the basal metabolic rate were +9%, +2%, and —7%. Fifty minutes after an Ewald test meal there were 10 degrees of free acid and 38 degrees of total acid. The stools contained no parasites except for Trichomonas hominis (a few organisms), no blood, and a minimal amount of undigested starch, fat, and protein. Skin tests for Trichinella and Echinococcus gave negative results.[6] Blood guanidine measured 0.21 mg. per 100 cc., determined as methylguanidine. Cholesterol measured 242 and 255 mg.; amylase, 72 units; glutathione, 36.8 mg., and ascorbic acid, 0.8 mg., per 100 cc. There were no porphyrins. The prothrombin level, in nine estimations, was uninfluenced by injection of vitamin K intramuscularly, the average being 93% of normal with the two-stage method. Nonprotein nitrogen measured 35 mg.; uric acid, 3.5 mg.; creatinine, 1.3 mg.; chlorides, 530 mg.; phosphorus, 3.8 mg., and calcium, 10.0 mg., per 100 cc.

Administration by mask of oxygen in concentrations up to 50% for four hours did not result in any change in the muscular twitching. Aminoacetic acid (glycine), administered over several months, improved the patient's sense of well-being but did not modify the two chief complaints.

Three glucose tolerance tests with 100 gm. of glucose given orally on a fasting stomach yielded the following data:

	Blood Glucose, Mg./100 Cc.		
	First Test	Second Test	Third Test
Fasting	91	91	90
½ hr.	183	160	189
1 hr.	154	169	127
2 hr.	60	95	100
3 hr.*	40	40	96
4 hr.†	69	64	83

* Taken ½ hour after the beginning of the hypoglycemic episodes.
† Fifteen minutes after subcutaneous injection of 1 cc. of epinephrine hydrochloride, 1: 1,000.

One qualitative test of the urine for reducing substances gave a negative reaction every hour.

A fructose (levulose) tolerance test, with 50 gm. given by mouth on a fasting stomach, showed the following values:

	Blood Fructose, Mg./100 Cc.
Fasting	97
40 min.	133
70 min.	148
1½ hr.	137
2½ hr.	129
3½ hr.	118

Serum sodium-potassium and calcium-phosphorus ratios were determined before and 72 hours after administration of a Wilder test diet with low-sodium and high-potassium content.

	Before Diet	After Diet *	After Adrenal Cortex †
Sodium, mEq.	147	143	139 (321 mg./100 cc.)
Potassium, mEq.	4.11	5.63	3.76 (14.7 mg./100 cc.)
Calcium, mg./cc.	...	10.0	.....
Phosphorus, mg./100 cc.	...	3.8	.....
Total base, mEq.	167	167	.....

* Calcium gluconate, 4 gm. four times a day orally, was ineffectual in relieving complaints.
† Adrenal cortex extract, 15 cc. subcutaneously daily, was given for six days. Each cubic centimeter contained activity from 75 gm. fresh tissue, assayed to 4 rat units per cubic centimeter.

6. The skin tests were performed by Dr. Marion Hood.

The hippuric acid conjugation test, with 5 gm. of benzoic acid given by mouth at 8 a. m. on a fasting stomach, showed 0.831, 1.291, 1.268, and 0.819 gm., calculated as benzoic acid, in the 9-, 10-, 11-, and 12-o'clock urines, respectively, the amount recovered totaling 4.209 gm.

The insulin sensitivity test, with 8 units (0.123 unit per kilogram of body weight) injected subcutaneously, gave the following values: fasting blood sugar, 85 mg. per 100 cc.; blood sugar 90 minutes later, 43 mg. per 100 cc. Epinephrine was required to interrupt the hypoglycemic episode. In 1934, at Clifton Springs Sanitarium, 5 units of insulin was administered before each meal for over one week to increase the appetite, but its use was discontinued on account of the occurrence of drenching perspiration two to three hours after each meal.

Administration of "phyone," a preparation (20 rat units per cubic centimeter) of the growth-promoting principle of the anterior lobe of the pituitary, up to 10 cc. subcutaneously per day for seven days, followed by oral administration of ascorbic acid, 100 mg. three times a day for 14 days, failed to influence the episodes or the fasciculations. Thiamine hydrochloride, 50 mg. per day injected subcutaneously in single doses for 21 days, followed by nicotinic acid, 150 mg. daily given orally for 4 days, and ephedrine sulfate, 1/8 grain (0.024 gm.) three times a day for 3 days, exhibited no effect. Alphatocopherol (ephynal®), 150 mg. per day given by mouth for 10 days, resulted in no alteration of the fasciculations.

A diet of 3,500 calories, divided into four-hour feedings, tolerated for 15 days, raised the body weight from 146 to 151 lb. (66.2 to 68.5 kg.) but did not alter the fasciculations. Hypoglycemic episodes were much diminished but returned again with anorexia, forcing a corresponding reduction in food intake, then a drop in weight to the previous level. The weight in December, 1940, was maintained at 142 lb. (64.4 kg.) on a 2,200-calory diet, with 100 gm. of protein in five to six feedings per day, without episodes.

The blood pressure was uninfluenced by any of the above tests or medications, remaining 80 to 110 systolic and 60 to 70 diastolic in both arms.

Surgical exploration was undertaken on Nov. 19, 1940, by Dr. Edwin Miller to locate and eliminate any organic lesion of the pancreas. Because of previous surgery, including cholecystectomy and gastroenterostomy, the pancreatic approach was formidable and extremely hazardous. No tumor or hypertrophy was seen. The condition of the patient and the overlying position of the splenic artery made biopsy of the pancreas inadvisable. Biopsy of liver tissue revealed normal architecture of liver cells and portal spaces. Chemical assay of the fresh liver revealed 41 mg. of glycogen per 100 gm. of fresh wet tissue. Biopsy of the right gastrocnemius muscle revealed normal histologic structure and 44 mg. of glycogen per 100 gm. The specimen of muscle displayed no fibrillation during or after removal. Anesthesia was induced with ethylene and ether. No fibrillation appeared in any muscle group inspected during the anesthesia, nor was it visible until 36 hours after operation, when it was again seen first in both gastrocnemius muscles, spreading to other muscles within a week. Convalescence was uneventful and was quite free from hypoglycemic episodes while the patient was receiving a 2,200-caloric diet and 1,000 cc. of 5% glucose in isotonic sodium chloride solution per day intravenously.

In July, 1950, the Hanger test gave a negative reaction.

An intravenous glucose tolerance test, with 0.5 gm. per kilogram of body weight administered as 20% glucose solution in distilled water in 10 minutes, showed the values for blood sugar tabulated. The test was repeated in 48 hours, preceded by administration of 1/150 grain (0.40 mg.) of atropine sulfate subcutaneously three times at six-hour intervals, with the results indicated in the tabulation.

	Glucose Tolerance Values	
	Without Atropine	After Atropine
Fasting	70	64
½ hr.	220	127
1 hr.	147	184
2 hr.	74	195
3 hr.	56	74
4 hr.	80	56

A clinical hypoglycemic reaction punctuated the 56 mg. reading in each test. Fasting blood amylase was 48 units per 100 cc.[7] Sensitivity to corticotropin (ACTH) was estimated as follows:

	Blood Uric Acid/ Creatinine, Mg. per 100 Cc.	Absolute Eosinophile Count, %	Cholinesterase,* Cu. Mm.	
Before corticotropin	0.060/0.160	198.0	....	
4 hr. after 25 mg. corticotropin was injected intramuscularly	0.103/0.162	11.5	....	
			Plasma	Red Blood Cells
Before corticotropin	.....	.....	26.9	80.0
5 hr. after 50 mg. corticotropin was given intramuscularly	.....	.....	26.1	86.0

* The cholinesterase activity of plasma and red blood cells was estimated by Dr. J. A. Rider by the method of R. Ammon (Enzymatic Splitting of Acetylcholine, Arch. ges. Physiol. **233**: 486, 1930) as modified by Mazur and Bodansky (Mazur, A., and Bodansky, O.: Mechanism of in Vitro and in Vivo Inhibition of Cholinesterase Activity by Diisopropyl Fluorophosphate, J. Biol. Chem. **163**: 261, 1946). Readings represent cubic millimeters of carbon dioxide liberated in five minutes by 0.1 cc. of plasma or 0.2 cc. of a 25% red blood cell solution in sodium bicarbonate hydrolyzing a standard acetylcholine solution in bicarbonate buffer at 37 C. in the Warburg manometer. Correction for gas evolved was made by using a control without plasma or red blood cells.

Myograms of the left gastrocnemius were not altered by administration of 50 mg. of corticotropin intramuscularly.

Biopsy of the left gastrocnemius was done, with results to be described later.

Previous examinations reported to me follow:

1. Biopsy of the left gastrocnemius was done at the Mayo Clinic in 1932, when it was found that use of local anesthesia before injection of anesthetic, into the specimen after excision, and spinal anesthesia did not affect the twitching, though with the spinal anesthesia there was complete motor and sensory paralysis below the umbilicus. The phenomenon continued in the biopsy specimen for eight minutes. Histologic and chemical examination revealed no explanatory evidence.

2. Estimations of the basal metabolic rate, repeated from 1930, at the Mayo Clinic, through 1934, at Clifton Springs Sanitarium, showed values of —27 to —16%, the upper level being reached when the patient was receiving desiccated thyroid. Substitution therapy was discontinued because of sleeplessness, palpitation, and tremor of the hands.

3. Action current and pneumatic records and chronaximeter readings were made in 1934 by Stetson and Snodgrass[8] at Oberlin College, Ohio, on intact fibrillating and resting muscle and were compared with the normal. The painstaking inquiry included studies of the intercostal, diaphragmatic, and abdominal muscles for the cause of intermittent partial aphonia and weakness of the voice. I have been provided with these records, and I agree with the interpretation of the authors, particularly in the light of myograms made subsequently through facilities of Dr. Percival Bailey and Dr. W. S. McCullough. Coincidences either of contraction or of relaxation showing on action-current records taken synchronously on the two legs in homologous positions were no greater than would occur by chance. Even in the normal subject with or without a tremor there was no synchrony of the action-current bursts from the two legs. Pneumatic records taken from three points in a muscle group simultaneously during fibrillation showed no regular recurrence of contraction at a given point. Synchrony of the phases of relaxation in the three points, however, was much more frequent than would be expected from chance, or than occurred in the normal, and suggested an inhibitory pulse for the entire muscle. Chronaxie on the average seemed definitely shorter than normal, as demonstrated on the right and left peroneal and gastrocnemius muscles.

7. Blood amylase was determined by the method of Smith and Rose (Smith, B. W., and Rose, J. H.: J. Biol. Chem. **179**: 53, 1949).

8. Records were furnished by Drs. R. H. Stetson and J. M. Snodgrass. These tracings were compared with those of later dates, together with records on the two sons who submitted to muscle biopsy. Dr. Pauline Cook assisted in the interpretation of the myograms.

Electromyographic tracings of muscles of the right calf were made on Sept. 29, 1943, through the courtesy of Dr. Percival Bailey and Dr. W. S. McCullough, at the Illinois Neuropsychiatric Institute.

Three points each 2.5 cm. apart close to the inner head of the right gastrocnemius were tapped with needle electrodes. No synchrony was identified in the action bursts from the three points. There was no regularity in their occurrence from any point. The potential was very uniform for all bursts. Relaxation periods were also without uniformity either as to timing or in relation to other points.

In 1947, corresponding points at the inner head of the right and of the left gastrocnemius muscle were tapped with needle electrodes. There was no synchrony in action bursts from the two sides or in relaxation periods. Potentials ranged from 30 to 40 mv. Tubocurarine chloride U. S. P., 15 mg. intravenously, brought decrease in frequency and in voltage of action bursts until they ceased entirely. Muscle stretch failed to induce bursts. Neostigmine methylsulfate, 5 cc. of 1:2,000 solution given intravenously, induced full recovery of action bursts in both frequency and voltage.

In July, 1950, action bursts continued at a frequency of 2 to 4 per second of a 100- to 200-μv potential at rest. They advanced to a potential of 1,000 μv on stretch or cramp. No change took place in the bursts on maintenance for 10 minutes with a Tycos cuff of a pressure of 150 mm. Hg, just above blood pressure, on the thigh above the electrodes. Nor did hyperventilation following this alter these bursts. Two and one-half hours after intramuscular injection of 50 mg. of corticotropin there again was no modification of action bursts.

The basal metabolic rates in 1943 conformed closely to those of 1940, viz., —4 and +7%, while the patient was taking desiccated thyroid, 1 grain (0.065 gm.) daily. The question arises as to whether the constantly moving muscle fibers might not have maintained a metabolic rate sufficiently elevated to account for the higher rate then observed, in contrast to the low metabolic rate and less activity from 1930 to 1934. This question becomes more pointed as the rates of 1944 and 1950 remain in the normal range after discontinuation of thyroid.

Examination of Sons.—The eldest child, a son aged 30, 73 in. (190.5 cm.) in height, was reported by a competent medical examiner to be normal objectively except for notable slight twitchings of undulatory character in both gastrocnemius muscles. The blood cell count was entirely normal. The basal metabolic rates, determined four times, ranged from —7 to —12%. The glucose tolerance test gave normal values for glucose levels of the blood and urine and normal curves for the same. A history of rare cramps in the calf muscles was volunteered.

The second child, a son aged 27, 71 in. (185.4 cm.) in height and 185 lb. (83.9 kg.) in weight, was reported to be similarly normal except for undulatory twitchings in the calf and thigh muscles on both sides. Twitchings of the muscles of the eyelids were especially prominent in fatigue. The basal metabolic rate was —8%. The glucose tolerance test gave normal values and a normal curve. There was a history of rare cramps of the calf muscles.

The third child, a son aged 26, 72½ in. (189.3 cm.) in height and 152 lb. (68.9 kg.) in weight, showed a normal physical condition except for the undulatory unrest of muscles of the calves and occasional waves of fasciculation in the muscles of the upper arms and forearms and in the temporal muscles. These movements were not influenced by fatigue, sleep, mechanical stimulation, or anoxia, by application of the sphygmomanometer cuff at systolic blood pressure for five minutes, or by administration of quinine methochloride, 50 grains (3.25 gm.) every eight hours for four days. The glucose tolerance test, with oral administration of 100 gm. of glucose on a fasting stomach, showed 80 mg. of fasting blood sugar per 100 cc., 134 mg. of blood sugar at 30 minutes, 96 mg. at 60 minutes, 58 mg. at 120 minutes, and 70 mg. at 240 minutes. The basal metabolic rate was —8%.

The fourth child, a son aged 22, 69 in. (180.3 cm.) in height and 159 lb. (72.1 kg.) in weight, was physically normal in all respects. Occasional twitches of the fasciculi of both gastrocnemius muscles occurred after mechanical stimulation with percussion. The basal metabolic rate was —1%. The glucose tolerance test gave normal values and a normal curve.

Examination of the mother is irrelevant, and that of other antecedents than the father has been impossible.

Histologic Studies.—Biopsies of muscle[9] from the father and from two of the sons was undertaken. The first biopsy, performed in 1940 on the father with conventional techniques by

9. Biopsy specimens were secured through the courtesy of Dr. Hillier L. Baker.

the late Dr. Carl Apfelbach, revealed no abnormal cytologic features except for "myositis" and "perimyositis," in agreement with my report for 1932 from the Mayo Clinic. The next muscle biopsies were done on the father and on the fourth son on July 27, 1944, with minimal procaine anesthesia of the skin and no other medication, a piece of muscle 1 cm. wide, 1 cm. thick, and 2.5 cm. long being secured from the left gastrocnemius and the left pectoralis major of each patient. Half of each specimen was processed by conventional technique in the department of pathology,[10] while the other half was processed by the late Dr. Eben J. Carey [11] and was studied by him in the department of anatomy, Marquette University School of Medicine, Milwaukee. A similar biopsy, with identical procedure, was carried out on the third son, on Dec. 16, 1946, the specimen being divided into two parts for work-up by the same two laboratories. The death of Dr. Carey has made impossible the correlation of this study with his long-term investigation of neuromuscular histology. At the department of pathology of the Presbyterian Hospital, we are unable to report any histologic abnormality in these specimens. The last biopsy was on the left gastrocnemius of the father, taken without local or general anesthesia or analgesia. One-half the tissue was used for study with the electron microscope,[12] and one-half, again, was studied by the department of pathology with conventional techniques, the two procedures yielding a similar report of normal muscle tissue. Ultramicroscopic study failed to reveal any abnormalities in either the basic structure of the myofibril or the sequence of structural changes during contraction induced with adenosinetriphosphate.

COMMENT

The involuntary twitching of muscle under study calls for its classification under four general types and for an examination of the anatomic structure and physiologic behavior of muscle.

Ford [13] described four types of muscle twitching: 1. True fibrillations, with contractions of individual muscle fibers, a result of complete destruction of the motor neurones, found in paralyzed muscle. Movements are minute and escape notice except when muscle is bared or covered by the thinnest skin. 2. Spontaneous fasciculation, not fibrillation, in progressive degeneration of neurones, which thus become the source of abnormal stimuli. This type is seen in progressive muscular atrophy from involvement of spinal motor nerves at any level. It is caused by the axon lesion. 3. Contraction fasciculation from loss of motor neurones. Normal contraction of voluntary muscle is the sequential shortening of small groups of muscle fibers to make a smooth total-muscle flexion. Loss of some neurones breaks the sequence and leaves isolated bundles of fibers in process of contraction. 4. Myokymia (μῦς, muscle; κῦμα, wave) is a local involuntary fascicular twitching of voluntary muscles, irregular in rate and in size of bundle, and usually undulatory. It seems not to be associated with atrophy or other incapacitating condition.

The present cases fall under the fourth type except that there is an element of fasciculation which shifts locally from one fiber group to another, as seen in the tongue, and diverse voluntary muscles, of widest distribution, are involved in the same patient. The term "myokymia" was first assigned by Schultze,[14] in 1895, to

10. Interpretations were made by Dr. George Hass.

11. Gold-chloride-teasing technique (Carey, E. J.: Studies on Ameboid Motion on Motor End-Plates, Am. J. Path. **18**:242, 1942).

12. Carried out by Dr. C. A. Ashley and Mr. B. E. Philpott at the Electron Microscope Laboratory, University of Illinois.

13. Ford, F. R.: Significance of Muscular Twitchings, Bull. Johns Hopkins Hosp. **64**:114, 1939.

14. Schultze, F.: Myokymie, Deutsche Ztschr. Nervenh. **6**:65-167, 1894-1895.

a group of cases in which there was wavy muscular twitching. The application was to a larger group, but included only those in which no organic lesion or cause was demonstrable and the condition was believed to improve or clear spontaneously.

In 1888 Kny [15] described two cases of fibrillary chorea under the name "myoclonus fibrillaris multiplex." He compared the disturbance in his cases with that of paramyoclonus multiplex, described by Friedreich [16] in 1881. Realizing that the type of twitching in his cases was not the same, he added fibrillaris to the name. Grund [17] cited cases and differentiated myokymia from known progressive organic disease processes. He followed Bittorf [18] in believing that the disturbance is in the motor end-plate or in a variation in response of the sarcoplasm and that it is manifest in delayed after-discharge. No details of tests were included. Bailey,[19] in 1925, reported a case of myokymia. De Vries,[20] in Java, reported a case and summarized 13 cases recorded up to 1937. In most instances the onset was preceded by an infection or intoxication. There was great variability in muscle response to mechanical and electrical stimulation. In none of the cases were hereditary characteristics noted. Wilder [21] insisted on the great frequency of myokymia in cramps of various sorts, especially in myoclonia.

Frey,[22] in 1930, reported on the examination of 100 persons, the offspring of one woman, born in 1792, reaching through five generations, 55 of whom possessed a muscle quiver of the chin. In a considerable number it began at birth and continued through life. In some the tremor was present continuously, night and day, in others, it occurred only on excitement or during emotional stress. In one group, the members possessing the quiver were asthenic, with small bone structure, easily fatigued muscles, and greater need for sleep than normal. In another group the opposite was true. No other muscular twitching was noted. No instances were found in which both mother and father carried the trait. Most of the affected members possessed an unusual sensitiveness to alcohol, manifested by vertigo and nausea, without, however, other muscle tremor. No one with minor quiver had descendents with frequent quiver; only slight quiverers and nonquiverers were found in his posterity. Most quiverers were healthy and long-lived. No case of epilepsy or degenerative nervous disease was found. Ganner,[23] in 1938, reported 33 chin quiverers, all members of two families of five generations. The ancestors of one family and an ancestor of the other had a common pair of grandparents, born in 1761. This chin quiver represents a stereotyped movement related to the tics.

15. Kny, E.: Myoclonus fibrillaris multiplex, Arch. Psychiat. **19**:577, 1888.

16. Friedreich, N.: Paramyoklonus Multiplex, Arch. path. Anat. **86**:421, 1881.

17. Grund, G.: Über genetische Beziehungen zwischen Myotonie, Deutsche Ztschr. Nervenh. **146**:3, 1938.

18. Bittorf, A.: Zur Kenntnis der Muskelkrämpfe peripheren Ursprungs und verwandter Erscheinungen, Deutsche Ztschr. Nervenh. **39**:208, 1910.

19. Bailey, P.: Myokymie, Rev. neurol. **1**:41, 1925.

20. de Vries, E.: Chorea Fibrillaris (Morvan) Myokymia (Schultze's), Psychiat. en neurol. bl., 1937, p. 96.

21. Wilder, J.: Myokymie, Myoclonie, Nervenarzt **8**:464, 1935.

22. Frey, Egon: Ein streng dominant erbliches Kinnmuskelzittern, Deutsche Ztschr. Nervenh. **115**:9, 1930.

23. Ganner, H: Erbliches Kinnzittern in eines Tiroler Tolschaft, Ztschr. ges. Neurol. u. Psychiat. **161**:259, 1938.

The origin of fasciculations is one of the objects of this study. Denny-Brown and Pennybacker [24] pointed out that the unit structure of muscle fiber is 3 to 5 cm. in length and 0.01 to 0.10 mm. in diameter, the length reaching 12 cm. in the platysma, and that the separate structures are without syncytial interconnection. These fibers are grouped into fasciculi, which become 2 to 10 mm. in diameter. Each ordinary fiber receives one motor end-plate, rarely two, perhaps from the same nerve fiber. Section of a particular motor nerve or its root results in degeneration of that nerve. Groups of muscle fibers degenerate, usually in the same fasciculus. One nerve fiber supplies up to 150 muscle fibers. The motor unit consists of the anterior horn cell, the axon and the dependent group of muscle fibers. Such a group continues alone in all-or-none fashion. Fine fibrillation occurs when the fasciculus is deprived of its nerve supply. Fasciculation does not occur. The fifth day after denervation twitching begins in a few fibers; by the seventh day it is present in all, until the muscle is in an advanced state of wasting, the fasciculation continuing at least 71 days. Twitching is entirely incoordinate. One action current is repeated at intervals of about 2/5 second. Experimentally, true fibrillation seems to be due to the sensitization of denervated muscle fiber to the small amounts of acetylcholine in the circulating blood. Fibrillation due to acetylcholine, as shown by inhibition of the natural destruction of this substance in the tissues by physostigmine, seems identical with spontaneous fibrillation. These authors believed that the gradual, indistinguishable transition from acetylcholine contracture to fibrillation indicates that the latter is only a very mild degree of the former and that smaller amounts of the substance must be present in the circulation. Myokymia, in their experience, has been associated with hyperidrosis and related to muscular cramps appearing with fatigue or loss of sodium chloride.

Sheldon and Woltman [25] described a case of amyotrophic lateral sclerosis in which spinal anesthesia, local anesthesia, and biopsy of gastrocnemius muscle were carried out. They believed that even in this disease the cell bodies of the anterior horn cells are excluded in the production of fasciculation. Experiments cited indicate that future studies should be addressed to peripheral portions of the neuromuscular unit, rather than to the cell body itself.

Harvey and MacIntosh [26] concluded that calcium is necessary to the action of potassium in liberating acetylcholine from the nerve endings. Impairment of transmission at the myoneural junction was observed by Brown and Harvey [27] in young animals kept on a diet deficient in calcium.

Grinker [28] concluded that the possibility exists that fasciculations are not central in origin but are evidence of a disordered muscular metabolism, secondary to the loss of the tropic influence of the anterior horn cells.

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24. Denny-Brown, D., and Pennybacker, J. B.: Fibrillation and Fasciculation in Voluntary Muscle, Brain **61**:311, 1938.

25. Sheldon, C. H., and Woltman, H. W.: Origin of Fibrillary Twitchings, Proc. Staff Meet., Mayo Clin. **15**:646, 1940.

26. Harvey, A. M., and MacIntosh, F. C.: Calcium and Synaptic Transmission in Sympathetic Ganglion, J. Physiol. **97**:408, 1940.

27. Brown, G. L., and Harvey, A. M.: Effects of Changes in Dietary Calcium on Neuromuscular Transmission, J. Physiol. **97**:330, 1940.

28. Grinker, R. R., and Levy, N. A.: Neurology, Springfield, Ill., Charles C Thomas, Publisher, 1943, p. 1037.

Gammon [29] and associates reviewed the literature on the nature of certain diseases of the voluntary muscles. They differentiated fasciculation from fibrillation simply on the basis that the former is a grossly visible movement. There is irregular twitching of muscles, often repeated and sometimes at random. The twitch involves a considerable number of fibers, which, contracting simultaneously, give rise to a local contraction easily visible through the skin. The same group of fibers may respond repeatedly as a unit. Denny-Brown and Pennybacker [24] called the movement "the single-impulse contraction of a fixed group of muscle fibers." The twitching is the result of the reception of a nerve impulse by the whole group—some hundred fibers supplied by a motor nerve fiber. Origin of the impulse is in axon or cell body. Myokymia is said by these authors to occur in normal persons and to have no pathologic significance. The contraction here is more sustained than the fascicular twitch and is often associated with a burst of action potentials rather than with a single response. Absence of spinal-cord disease and frequency of muscle cramps in myokymia bring their suggestion that the disturbance is a local one, due to ionic or circulatory changes within the muscle. Russel and associates [30] found that nerve and spinal blocks in amyotrophic lateral sclerosis did not abolish the twitching; so they proposed that the abnormal impulses arise in nerve ending or muscle. Grund,[17] on the same premises deduced that the nerve impulse causing the twitch often originates in the axon and does not come from within the spinal cord.

Fasciculation has been greatly increased, indeed initiated, by neostigmine. In a preparation by Masland and Wigton [31] showing active fasciculation as a result of neostigmine, administration of curare resulted in prompt cessation not only of muscle movement, but of antidromic impulses in the anterior root as well. This occurred with doses of curare insufficient to abolish indirect excitability of the muscle. Curare stopped nerve activity when it stopped visible muscle twitching; and always when it stopped the latter, it stopped the former. Eccles [32] also observed this effect and concluded that the site of action of these two substances is the same. Fasciculation may be stopped by small doses of curarizing substances. Quinine methochloride administered intra-arterially caused twitching to cease in the limb injected in a case of fasciculation due to spinal-cord disease observed by Harvey,[33] in which curarization was insufficient to accomplish neuromuscular block. While it has been shown that in periodic family paralysis attacks occur with a lowering of serum potassium without there being a corresponding excretion, but with a demonstrable shift to muscles,[34] neither the relation to acetylcholine and cholinesterase nor the site at

29. Gammon, G. D.; Harvey, A. M., and Masland, R. L.: On the Nature of Certain Diseases of Voluntary Muscles, Biol. Symposia **3**:291, 1941.

30. Russel, C. K.; Odom, G., and McEachern, D.: Physiological and Chemical Studies of Neuromuscular Disorders, Tr. Am. Neurol. **64**:120, 1938.

31. Masland, R. L., and Wigton, R. S.: Nerve Activity Accompanying Fasciculation Produced by Prostigmin, J. Neurophysiol **3**:269, 1940.

32. Eccles, J. C., and MacFarlane, W. V.: Actions of Anticholinesterases on End Plate Potential of Frog Muscle, J. Neurophysiol. **12**:59, 1949.

33. Harvey, A. M.: Action of Quinine Methochloride on Neuromuscular Transmission, Bull. Johns Hopkins Hosp. **66**:52, 1940.

34. Gass, H.; Cherkosky, M., and Savitsky, N.: Potassium and Periodic Paralysis, Medicine **27**:105, 1948.

which potassium is effective is fully explained. Potassium chloride, 3 gm. per day given by mouth for five days, was no longer tolerated in our case; yet no subjective or objective change occurred in the fasciculation.

Certain drugs of known potency and points of attack have given surprisingly varied responses when applied to the neuromuscular junction. An explanation for this is a contribution of Nachmansohn.[35] Though the flow of the stimulus from the origin along the nerve to the effector may be of the same nature, "chemical-electrical," not either/or, but an integration of the two, this flow is modified, at least in its transmission across the synapse, or neuromuscular junction, by qualitative or quantitative differences in the anatomic structure of barrier membranes around nerve or the material extruded by the nerve or muscle. Thus, iodized-oil-containing membrane permits passage of lipid-soluble physostigmine, strychnine, diisopropyl fluorophosphate, or procaine and bars penetration of water-soluble neostigmine, curarine, or acetylcholine. This is a far-removed corollary of Claude Bernard's century-old observation that curare, whose active principle is a methylated quaternary ammonium salt, acts solely upon the neuromuscular junction.

The muscle biopsy has been notoriously unsatisfactory in giving uniform visualization of nerve fibrils, capillary network, and nerve endings with muscle connections. The physiologic approach has been far more successful. It, too, would be more valuable with sharp visual delineation of histologic shifts that parallel functional, stress, systemic, and focal pathologic states. The most recent attack in this direction was that of Carey,[36] who climaxed his years of neuromuscular investigations with a thesis on ameboid motion and secretion of motor end-plates. Without enumerating the revolutionary claims and suggestions in this paper, to which I can give no personal substantiation except the study of his sections, it must be stated that the logic and conclusions are not in opposition to the recorded physiologic evidence for the mechanism of transmission of the nerve impulse. The highly dynamic nature of the process makes it imperative to an understanding of structural dynamics that the processes be registered instantaneously in as many different stages of change as possible. Realization of this fact would particularly clarify thinking and therapeutics in the field at hand.

The mechanisms involved in chemical-electrical transmission, with the implications of acetylcholine, epinephrine, and related compounds, the shifting balance of cations and anions, the shifting phases and molecular rearrangement of nerve and muscle proteins and lipids, thermodynamics and energy transfers, fuel and metabolic logistics, intricate pharmacologic effects of unnaturally occurring compounds in various concentrations and combinations, catalyst and enzyme accelerators and arresters, and resultant or coincident changes in electric potentials—even this brief list hints at the unanticipated complexities involved in attempting the solution of just one segment of the unknown. Here, as in politics, we stand in need of a penetrating thinker and a cooperating team to help us see more clearly.

35. Nachmansohn, D.: Axonal Conduction and Synaptic Transmission, in Metabolism and Function, Houston, Texas, Elsevier Pub. Co., 1950.

36. Carey, E. J., and others: Studies on Ameboid Motion and Secretion of Motor End-Plates: VI. Pathologic Effects of Traumatic Shock on Motor and Sensory Nerve Endings in Skeletal Muscle of Unanesthetized Rats in the Noble-Collys Drum, Am. J. Path. **21**:935, 1945.

Studies on the cases here presented suggest that (1) the source of stimulation in fasciculation does not lie in the cord or in the axon; (2) the mediating mechanism may be in a metabolic defect situated in, or peripheral to, the neuromuscular junction, proximal to the myofibrils; (3) there is no structural deviation from the normal muscle fibrils as identified by search with the electron-microscope; (4) there is probably no timing device in the metabolic-chemical chain of muscle-fascicle response, though there may be in relaxation; (5) in the cases presented an inherited error in the metabolic-chemical relationship may have been focused in voluntary muscle-fascicle units; (6) there is a concomitant metabolic disturbance of the thyroid and of the glucose-utilization mechanism in the father and to a less degree, in the four sons, in their present age relationships.

GERSTMANN SYMPTOMS FOLLOWING ELECTROSHOCK TREATMENT

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IN A RECENT communication, Juba [1] has reported the occasional occurrence of the various elements of the Gerstmann syndrome (finger agnosia, right-left disorientation, agraphia, acalculia) as an immediate consequence of electroshock treatment in psychiatric patients. The typical picture is described as follows: After the cessation of convulsions and the clearing of consciousness, and at a time when the patient is personally oriented (i. e., is able to give his name, date and place of birth, residence, etc.), is able to name colors and a variety of objects, and can identify various parts of his body (nose, mouth, eyes, etc.), he may show a striking inability to point out or name his fingers when requested to do so. In some cases the finger agnosia is accompanied by one or more of the other elements of the Gerstmann syndrome—right-left disorientation, agraphia, and acalculia. Further, at this time the behavior of the patient clearly indicates some degree of space and time disorientation. Finally, the *Simultanagnosie* of Wolpert,[2] i. e., inability to perceive the central theme of a picture or the action represented in it, with preservation of the ability to perceive the details in it, was consistently observed in these patients.

Five case reports, all of women, are included in the paper. The essential findings with respect to the elements of the Gerstmann syndrome are summarized in Table 1.

Juba is of the opinion that, in view of current concepts of the neuroanatomic substrate of the Gerstmann syndrome, these post-electroshock behavioral disorders may be considered focal symptoms of parieto-occipital dysfunctions. In line with current tendencies in psychoneurologic theorizing, he is inclined to "explain" the diverse disabilities by reference to a single unitary principle. Thus, he considers that the

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1. Juba, A.: Über nach Electroschock auftretende kortikale Funktionsstörungen (Gerstmann'sches Syndrom, Gesichts- und Raumagnosien), Schweiz. Arch. Neurol. u. Psychiat. **61**:217-226, 1948.

2. Wolpert, I.: Die Simultanagnosie—Störung der Gesamtauffassung, Ztschr. ges. Neurol. u. Psychiat. **93**:397-415, 1924.

finger agnosia, difficulties in visual perception, right-left disorientation, and other disabilities are expressions of a single, basic impairment in Gestalt formation, or "globalizing function."

The purpose of the present investigation was essentially to attempt to verify Juba's findings with respect to the occurrence of the Gerstmann elements following electroshock. If his findings could be verified, we proposed to examine particularly the nature of the grouping of the symptoms and to consider its implications for the various theoretical principles which have been proposed as explanations for the association of these rather diverse behavorial deficits.

INVESTIGATIVE METHOD AND REPORT OF A CASE

Method and Material.—The subjects were psychotic men, most of whom carried diagnoses of schizophrenia, who were hospitalized at the Knoxville Veterans Administration Hospital and were undergoing electroshock treatment. The investigative procedures employed in the study can best be described by citing a concrete case. The protocol follows.

TABLE 1.—*Essential Findings in Juba's Investigation of Gerstmann Syndrome*

Case No.	Finger Agnosia		Right-Left Disorientation			
	Own Hands	Examiner's Hands	Own Body	Examiner's Body or Objects	Acalculia	Agraphia
1	Severe	.....	None	.....	Severe	None
2	Severe	.....	Severe	.....	None	Moderate
3	Severe	.....	Moderate	None	Severe	Slight
4	Severe	.....	None	None	None	None
5	Severe	Severe	Moderate	None	....	....

A. M., aged 28; diagnosis, "schizophrenic reaction, mixed type, manifested by auditory hallucinations, vague delusions of persecution, and thinking defect"; 13th electroshock treatment, Monday, May 21, 1951.

8:22 a. m. Electroshock convulsion.

8:28 a. m. Turns when name is called.

8:31 a. m. Says "Huh?" when name is called.

8:34 a. m. Gives last name when name is asked.
Gives first name when asked it.
Gives first name when asked his full name.
Gives full name when asked it.
Gives full name when asked it again.

8:39 a. m. When asked how old he is, says, "I don't know . . . about 23 . . . I don't know . . . about 25."
Asked where he is, says, "I don't know."
Asked the time, says, "I don't know."

8:41 a. m. Asked how old he is, says, "About 26, 25, 27 . . . something like that."

8:42 a. m. When requested, correctly points to nose, chin, and mouth.

8:43 a. m. Asked what time it is, says, "I don't know."
Asked how old he is, says, "28."

8:44 a. m. Right-left orientation. On request, correctly shows his right hand, left leg, and left eye; then shows left ear for right ear; then shows right hand for left hand, but spontaneously corrects his response. Requested to point to examiner's right hand, points to the latter's left hand; requested to point to examiner's right leg, looks over examiner's body but makes no response; requested to point to examiner's left eye, responds correctly; requested to point to examiner's right ear, looks at examiner but makes no response.

When examiner points to patient's left hand and asks, "Which hand is this?" patient names it correctly; similarly, names correctly his right ear, right leg, and right hand. When examiner points to his own right hand and asks, "Which hand is this?" patient names it correctly; similarly, correctly names examiner's left ear; then incorrectly names examiner's left leg; finally, names correctly examiner's left hand.

8:48 a. m. Asked what day of the week it is, says, "Monday" (correct).
Asked what month it is, says "Tuesday."
Asked what year it is, says, "Tuesday."

8:49 a. m. Finger localization and naming. Patient's right hand, palm up: Asked to show his thumb, patient responds correctly; asked to show his little finger, patient first shows thumb, then responds correctly; asked to show middle finger and ring finger, patient responds correctly.
Left hand, palm up: Asked to show little finger, patient shows index finger; asked to show thumb, middle finger, ring finger, responds correctly. Examiner's left hand, palm up: Asked to point to examiner's thumb, patient responds correctly; asked to point to examiner's middle finger, responds correctly; asked to point to examiner's little finger, first points to thumb, then responds correctly; asked to point to examiner's ring finger, responds correctly.

8:52 a. m. Given one- and two-digit numbers to read, patient does it without difficulty. Calculation: Asked orally to add 4 and 2, patient answers correctly; asked orally to add 6 and 3, says "7"; given the addition problem written on a card, answers correctly. Asked orally to add 14 and 5, he says "9"; given the addition problem written on a card, says, "Uh, 14 and 5? . . . that's, uh . . . uh, 6 . . . uh, 5." Asked orally to add 8 and 6, he answers correctly. Asked to subtract 3 from 5, patient says, "7, 3 is . . . uh . . . 15"; given the subtraction problem written on a card, answers correctly; asked to subtract 4 from 9, says, "12? . . . 13?"; given the subtraction problem in written form, says, "3 . . . 13?"; asked to subtract 8 from 17, says, "17 from 18 . . . ?"; given the subtraction problem in written form, answers correctly. Asked to multiply 4 by 2, he answers correctly, asked to multiply 5 by 3, says, "is 8 . . . is 15"; asked to multiply 7 by 4, says, "16"; given the multiplication problem in written form, answers correctly. Asked to multiply 6 by 3, he says, "28 . . . 28"; given the multiplication problem in written form, answers correctly. Asked to divide 6 by 3, says, "18"; given the problem in written form (in which the division operation is clearly indicated), again says, "18." Asked to divide 8 by 2, says, "12"; given the problem in written form, says, "16," then adds, "I don't know what the hell's the matter with me." Asked to divide 18 by 3, says, "24"; given problem in written form, says, "36." Asked to divide 32 by 4, says, "76"; given problem in written form, says, "96."

9:02 a. m. Given two simple sentences to read, patient does it without difficulty.
Writing: Requested to write his name, he asks if he should print or write. Told to do as he prefers, he writes name in cursive script; two letters of last name are run together, so that they are illegible. Asked to copy, I AM HUNGRY (printed in block letters on a card), he copies it fairly well in cursive script and includes the word "COPY," which was at the head of the card (Figure, *A*). Asked to write to dictation, "This is a nice day," he writes, "This is is a nice day day Day," with some difficulty in writing movements evi-

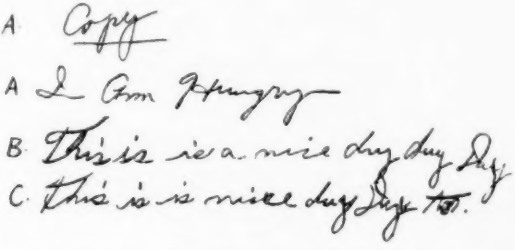
dent in the failure to form the *a's* in "day" and the directional confusion in the last word (Figure, *B*). Asked to write anything that occurred to him, he hesitates, then writes, "This is is mice day Day too," with some difficulty evident in the direction of writing movements (Figure, *C*).

9:06 a. m. Asked what time it is, says, "About half-past nine."
Asked what month it is, says, "I don't know."
Asked if it is spring, summer, winter, or fall, he says, "Spring" (correct).

9:09 a. m. Asked what month it is, says, "January?"

This case exemplifies the examination procedures employed. Right-left orientation and finger localization capacity were investigated only after the patient could point out his nose, chin, and mouth, i. e., after it had been determined that the patient was not suffering from a general autotopagnosia. Similarly, arithmetical calculation was assessed only after it had been determined that the patient could read one- and two-digit numbers, and samples of copying, writing to dictation, and spontaneous writing were obtained only after the patient had demonstrated capacity to read simple sentences.

Patient A. M. recovered his personal orientation (name, age) relatively rapidly after the convulsion. Twenty minutes after the seizure he was able to point out his nose, chin, and mouth when requested. Right-left orientation was then evaluated. He made two errors in nine tests of right-left orientation with respect to his own body, one of these errors being spontaneously



Writing of Patient A. M.: (*A*) Patient copies "I am hungry" and includes word, "Copy", which was on card; (*B*) writes to dictation, "This is a nice day"; (*C*) writes spontaneously.

corrected. He was rated as showing a "slight" degree of left-right disorientation with respect to his own body. He made four errors in eight tests of right-left orientation with respect to the examiner's body. The degree of disorientation in this situation was rated as "severe."

With respect to localization of his own fingers, the patient made two errors in eight tests, one of these errors being spontaneously corrected. He was rated as showing a slight degree of finger agnosia with respect to his own finger schema. He made one error (spontaneously corrected) in four tests of localization of the examiner's fingers. The degree of disability in this function was rated as "slight."

With respect to calculation, 12 of 16 simple problems were failed when presented orally. Seven of these problems were failed even when presented in written form. There was seemingly complete loss of the concept or process of division. The disability in calculation was rated as "severe."

He was able to write from copy but showed errors (repetitions, misspelling, misdirection of writing movements) in writing from dictation and spontaneous writing. The degree of impairment in writing was rated as "moderate."

Order of Administration.—Two different orders of administration of the tests were utilized. Order A, used with the first 20 patients, was as follows: (1) personal orientation; (2) body orientation (nose, chin, mouth); (3) right-left orientation; (4) finger localization; (5) reading numbers; (6) arithmetic calculation; (7) reading simple sentences; (8) writing. Order B, which was used with the second group, of 10 patients, was as follows: (1) personal orientation;

(2) reading simple sentences; (3) writing; (4) body orientation; (5) finger localization; (6) right-left orientation; (7) reading numbers; (8) arithmetic calculation.

Control Examination.—Each patient was given the entire battery of tests at some time during the interim period between shock treatments and not less than 24 hours after the last shock treatment.

RESULTS

Patients.—Satisfactory protocols were secured on 30 patients.[3] Sixteen patients did not show elements of the Gerstmann syndrome under the conditions employed in the present study, i. e., finger agnosia or right-left disorientation in the absence of a more general autotopagnosia, and acalculia or agraphia in the absence of alectic disturbances. Fourteen patients showed evidence of one or more of the Gerstmann elements. The findings are detailed in Table 2.

TABLE 2.—*Findings in Fourteen Patients Showing Gerstmann Elements*

	Finger Agnosia		Right-Left Disorientation			
Case	Own Hands	Examiner's Hands	Own Body	Examiner's Body or Objects	Acalculia	Agraphia
Order of Administration A: Right-Left Orientation; Finger Localization; Calculation; Writing						
A. S. M.	Slight	Slight	Slight	Severe	Severe	Moderate
F. D. A.	None	None	None	None	Slight	Moderate
E. J. B.	None	None	None	Severe	Moderate	None
W. C.	None	Slight	Slight	Moderate	Slight	None
G. R.	None	Severe	None	None	Moderate	None
R. S.	Moderate	None	None	None	None	None
R. J. S.	None	None	None	Moderate	None	None
L. W. C.	None	None	None	Moderate	None	None
Order of Administration B: Writing; Finger Localization; Right-Left Orientation; Calculation						
C. M. B.	None	None	Moderate	Slight	Slight	Severe
P. R.	None	None	Slight	None	Slight	Severe
R. M.	None	None	None	None	Severe	Moderate
R. I.	None	None	None	None	Mild	Moderate
C. S.	None	None	None	Severe	None	None
O. H. A.	None	None	None	Mild	Moderate	Moderate

Several conclusions are evident from the findings:

1. The results verify Juba's findings that Gerstmann symptoms in "pure form" (i. e., occurring independently, and not merely as part of a more extensive disturbance, for example, finger agnosia or right-left disorientation in the absence of a gross autotopagnosia, agraphia in the absence of alexia, and acalculia with preservation of the ability to read numbers) do occur as a feature of the temporary organic defect immediately following electroshock in some cases. In our sample, the proportion of patients exhibiting one or more Gerstmann elements approached 50%.

2. There are noteworthy differences in the frequency of occurrence of the individual symptoms. The most frequent single symptom was some degree of acalculia, which was manifested by 10 in the total group of 30 patients. The next most frequent symptom was some degree of right-left disorientation toward the

3. A total of 34 patients were examined, but 4 were not sufficiently cooperative to provide unambiguous data.

examiner's body, this defect occurring in eight cases. In contrast, right-left disorientation with respect to one's own body occurred in only four cases. The least frequent symptom was finger agnosia with respect either to one's own hands or to the hands of the examiner.

3. Order of administration of the tests during the postconvulsive period is possibly of significance in determining whether or not a Gerstmann deficit will be elicited. Thus, under the first order of administration (A), in which the writing tests were given last, the average time after shock being 25 minutes, only 2 of the 10 patients showed disturbances. In contrast, under the second order of presentation (B), in which the writing tests were given first, the average time after shock being 19 minutes, five of the six patients showed disturbances. One cannot have any real confidence that the observed difference here is not a chance one, due to fluctuating values in such small samples of cases. Indeed, the difference in the proportion of cases in the two groups showing any of the symptoms (40% in Group A versus 60% in Group B), which is presumably independent of the order of test administration, would favor a more frequent occurrence of agraphia in Group B and argue for the difference in incidence of graphic disturbances in the two groups being due to sampling error rather than to variation in order of presentation. Nevertheless, it is possible that this difference is a function of the order of presentation and reflects the extremely transient character of the postconvulsive agraphia.

Controls.—All but two patients showed no indication of Gerstmann symptoms in the control examinations given during an interim period between electroshock treatments. One patient showed a slight calculation difficulty. Since this was the only impairment he showed in the postconvulsive examination, he was considered to be a "negative" case, not showing postconvulsive Gerstmann symptoms. Another patient showed a slight dysgraphia in the control examination. In the postconvulsive examination he showed a somewhat severer dysgraphia; but since this was the only symptom shown, he too was considered to be a "negative" case.

COMMENT

Our results are fully confirmatory of Juba's contention that Gerstmann symptoms can be elicited in patients immediately after electroshock treatment. A detailed comparison of findings in the present study with those of Juba is not possible, since he provides data only for his five illustrative cases, and even here the reports are somewhat incomplete. One apparent discrepancy in results lies in the differences in the incidence of finger agnosia as a symptom. It was the symptom which was least frequently observed in our series of cases but was present in all of Juba's illustrative cases. Whether this difference is real or not is an open question. It is quite possible that Juba, considering finger agnosia to be the "nuclear symptom" of the syndrome, chose his illustrative cases with this deficit in mind.

This "experimental" production of Gerstmann symptoms through the medium of electroshock provides an opportunity to observe how the symptoms are grouped together in a Gerstmann "syndrome" and thus permits the possibility of evaluating the validity of some of the general principles which have been advanced to account for the concurrence of the symptoms.

There are first basic questions concerning the facts of the grouping itself. Are these behavorial deficits necessarily linked together in a unified configuration? How often do they appear in full combination? How often do they appear separately or in partial combination? If it were not for the rather imprecise use of the term in medical writing, the question might be phrased in the form of whether the behavioral phenomena involved really constitute a true "syndrome." It is fairly well established that these behavorial impairments do tend to occur together. However, a quantitative assessment of the strength of this "clustering tendency" has never been made, nor is there reliable knowledge about the closeness of association between the elements of different pairs of the symptoms. That significant differences may exist in this respect is suggested by Gerstmann's [4] original description of the syndrome, in which only finger agnosia and agraphia were designated as "cardinal symptoms," while the other behavorial deficits, such as acalculia and right-left disorientation, were classified as being merely "bordering symptoms," which might or might not be present.

A reasonably accurate answer to this question has decisive implications for an evaluation of the significance of the grouping of the symptoms. The significance of this grouping has been variously interpreted. The conception which has been advanced most frequently is that these behavioral deficits owe whatever communality with respect to incidence they may possess to the fact that they are all partial expressions of a single basic deficit. The basic deficit has been designated by different authors as an impairment in the "body schema," in "directional orientation," in the "conception of space," in the capacity to apprehend "figure-ground" relationships, etc. Typically, in support of one or the other explanatory principle, cases are reported in which it is demonstrated that in other areas the patient showed defective behavior referable to the hypothesized basic general impairment. Exceptions to the rule characteristically either are ignored or are classified as cases of "abortive" or "incomplete" expressions of the basic deficit.

Another idea which has been advanced, although in tentative, and occasionally vague, fashion, is concerned particularly with the association between finger agnosia and acalculia. It is proposed that the finger agnosia is the more basic deficit and is responsible for the acalculia in much the same sense that, for example, loss of appreciation of direction of lines drawn on the skin surface might be said to be responsible for "agraphesthesia" (loss of recognition of letters and numbers drawn on the skin surface). Recourse is usually made to genetic and cultural-anthropological data to support this contention, e. g., that the child learns to count by means of his fingers, that the number systems of some primitive cultures are limited by the total number of fingers and toes, that our own decimal system, as well as the word "digit," reflect this relationship.

A third point of view denies the cogency of any of these unitary explanatory principles and holds that the elements of the syndrome are not psychologically related in any fundamental sense, or at least that no such fundamental relationship has yet been demonstrated. In support of this contention, its proponents point to instances of the isolated occurrence of one or another element of the syndrome as indicating that the prediction of relatively widespread impairment demanded by

4. Gerstmann, J.: Fingeragnosie und isolierte Agraphie—Ein neues Syndrom, Ztschr. ges. Neurol. u. Psychiat. **108**:152-177, 1927.

any of the hypotheses which postulate a basic general deficit is not substantiated by clinical experience. The relative frequency of combined occurrence of the symptoms is explained by the close proximity of the cortical "centers" involved in each of the performances, this proximity making for a heightened probability that all or any combination of the "centers" would be simultaneously affected by cerebral injury or disease.

In utilizing the findings of the present study for an empirical evaluation of the cogency of these explanatory principles, one must give due consideration to the fact that these "experimentally" produced symptoms are of a transient nature. One must therefore consider the possibility that, in serial elicitations of symptoms, as in the procedure of this study, a symptom which was actually coexistent with another symptom might not be elicited because during the short time interval elapsing before it was investigated the patient had recovered the particular function. The net effect of such transiency would be to indicate a nonconcurrence of symptoms where actually such concurrence did exist. One extreme, already mentioned, is represented by the example of the writing tests, which were separated by an average interval of six minutes in the two orders of administration. The other two extreme examples are right-left orientation versus writing in order of administration A and writing versus calculation in order of administration B. However, inspection of the data indicates that the separation of a few minutes in giving the tests could hardly have affected the degree of concurrence of the symptoms. Thus, in order of administration A, there were only two examples of right-left disorientation to the subject's own body, despite the fact that this was the first test given. In order of administration B, a perfect concurrence in the appearance or nonappearance of agraphia and acalculia is evident, despite the fact that one was the first test given and the other the last. If temporal effects are not apparent in these extreme examples, it is not likely that they occurred with the other pairs of tests which were separated by smaller intervals of time. Therefore, it would seem reasonable, for practical purposes, to ignore the order of presentation of the tests in considering the empirical findings and their implications for a "theory" of the Gerstmann syndrome.

The first observation which may be made is that only 1 of the 14 patients showed all four of the Gerstmann deficits. This is in accord with the general tenor of the clinical literature, which indicates clearly that cases in which all four symptoms are shown make up a very small proportion of the cases. This single fact in itself would seem to have definite implications for any general theoretical principle which is advanced to account for the concurrence of the four symptoms. Nonconcurrence of the four symptoms is the rule, and concurrence is the exception. Therefore, there would seem to be little need for a "theory" to explain a "unity" which is far less often observed than is its opposite. Moreover, even if it be granted that it is desirable to have a principle to account for the occasional observation of concurrence of all four symptoms, such a principle must account satisfactorily for the far more numerous cases of nonconcurrence.

A comparison of the frequency of concurrence of the symptoms of finger agnosia and agraphia affords an opportunity to evaluate Gerstmann's original conception that these deficits form the "nucleus" of the syndrome. If these symptoms are basically related in any way, they should tend to occur together. Inspection of the data shows no indications of such a tendency. Agraphia was a relatively frequent

symptom (seven cases), while finger agnosia, with respect either to one's own hands or those of the examiner, was less frequent (four cases). Of the four patients showing finger agnosia, only one showed a concomitant agraphia. Clearly, there is no evidence of a significant relationship, even of moderate degree, between the two deficits.

Other pairs of symptoms show various relationships: 1. Acalculia and agraphia appear to be closely related. Of the 10 patients showing acalculia, 7 showed a concomitant agraphia. Stated in another way, all seven patients with agraphia showed a concomitant acalculia.

2. Finger agnosia and right-left disorientation show a questionable relationship. Of the four patients showing finger agnosia, with respect either to the subject's own hands or to those of the examiner, two showed a concomitant right-left disorientation with respect to both the subject's own body and that of the examiner. Of the three patients showing finger agnosia with respect to the examiner's hands, two showed right-left disorientation with respect to both the patient's own body and that of the examiner.

3. Finger agnosia and acalculia show a questionable relationship. Of the two patients with finger agnosia, only one showed a concomitant acalculia, despite the fact that the latter was the most frequent symptom observed. However, all three patients showing finger agnosia with respect to the hands of the examiner presented a concomitant acalculia.

Examination of the other pairs of symptoms yields evidence of no more than a chance relationship between the members of the pairs.

We have, then, indications of an impressive degree of relationship only between agraphia and acalculia. The common factor here may be that both functions belong to the area of language and symbolic behavior. However, before this idea can be accepted, it will be necessary to rule out a more parsimonious, alternative explanation, viz., that since both functions make greater intellectual demands on the patient than do finger localization or right-left orientation, their concomitant impairment is simply a resultant of the lower general level of psychological efficiency which is characteristic of the postconvulsive state.

The indication that there may be a relationship of moderate magnitude between the finger agnosia and the right-left disorientation is supported by the results of a previous investigation [5] in which a significant relationship between the two functions in brain-injured children was found. A unitary factor, such as the "body schema," may be invoked as an explanatory principle to account for the modest degree of the relationship, but it is evident that such a factor, while not meaningless, cannot be of very great importance. A similar situation exists with regard to the possibility that there may be some relationship between finger agnosia and acalculia. The degree of the suggested relationship is small, at best, and the investigation cited above [5] failed to yield evidence of any relationship between the two functions either in normal or in brain-injured children. It is doubtful whether this relationship would survive an attempt at verification.

5. Benton, A. L.; Hutcheon, J. F., and Seymour, E.: Arithmetic Ability, Finger-Localization Capacity and Right-Left Discrimination in Normal and Defective Children, Am. J. Orthopsychiat. **21**:756-766 (Oct.) 1951.

All in all, the findings point to specificity rather than to generality in the elements of the Gerstmann syndrome. They raise considerable doubt whether the four symptoms should be called a "syndrome," if by that term is meant a combination of symptoms which bear some lawful relation to one another. The observations indicate that there is no necessity for invoking a unitary general principle, such as "loss of conception of space" or "impairment in directional orientation," to account for the observed phenomena, since no empirical unity is apparent. The "instrumental" notion that finger agnosia determines acalculia is also found to be relatively superfluous in the absence of empirical demonstration of an important relationship between the two functions. In general, the results of the present investigation are consonant with a theory which is based on topographic considerations and which accounts for the observed tendency of these symptoms to occur together in terms of the "accident" of proximity of cortical "centers" rather than in terms of basic psychologic relationships.

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THE SCHIZOPHRENIC REACTION WITH PSYCHOPATHIC FEATURES: CLINICAL CHARACTERISTICS AND RESPONSE TO THERAPY

A Comprehensive Study of Seven Cases

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PRICHARD, in 1835, described "moral insanity" as a "form of mental derangement . . . in which the moral and active principles of the mind are strongly perverted so that the individual is found to be incapable . . . of conducting himself with decency and propriety in the business of life." [1] In 1888 Koch changed the name of this pathological entity to constitutional psychopathic inferiority. "Psychopathy" has been used as a "wastebasket" term since its introduction into the psychiatric nosology because its clinical characteristics and limits are so poorly defined. The term as used today describes "various inadequacies and deviations in the personality structure of individuals . . . the defect existing primarily in the conative, emotional and characterological aspects of the personality." [2] As a result of the vagueness of the concept of psychopathy, many patients have been classified as psychopathic who actually were neurotic or psychotic with psychopathic symptoms.

Karpman,[3] in search of a more specific definition of the boundaries of psychopathy, has divided it into two distinct subtypes: secondary, or symptomatic, psychopathy, cases of which compromise 85% of the total number, and primary, idiopathic, or essential psychopathy (anethopathy), representing the remaining 15%. In the first subdivision are included all those cases in which, in terms of overt behavior, the disorder seems to be classic psychopathy but in which psychogenic determinants are easily elicited and the psychopathic behavior reveals itself to be a "specific conditioned reaction." Under primary psychopathy are included patients in whom careful study fails to reveal "any deep psychic motivation" for their acting-out behavior. This report is concerned with a study of a group of patients falling into Karpman's symptomatic class of psychopathy, i. e., patients

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1. Prichard, J. C.: Treatise of Insanity, London, Sherwood, Gilbert and Piper, 1835.

2. Noyes, A. P.: Modern Clinical Psychiatry, Philadelphia, W. B. Saunders Company, 1939.

3. Karpman, B.: Passive Parasitic Psychopathy, Psychoanalytic. Rev. **34**:103, 1947.

who are schizophrenic but have exhibited a lifelong history of psychopathic behavior. Frequently, diagnosis in this group is difficult and open to dispute. However, Bleuler's [4] admonition is recalled:

> Inasmuch as yet we have no standard to tell us how pronounced the symptoms must be to enable us to assume a schizophrenic process . . . in psychopaths one will be careful not to want to exclude it.

In an attempt to evaluate further the clinical characteristics and response to therapy of this group, seven patients were selected for study. Summaries of their case histories follow.

CASE 1.—A white man aged 31 had been enuretic all his life. He was a quiet, timid, shy child during his preschool period. He disliked school, was a disciplinary problem, and frequently was truant. He was arrested at the age of 14 for petty larceny and got a suspended sentence. He served three enlistments in the Civilian Conservation Corps (CCC), the last two under a false name, and was given a dishonorable discharge for wetting a toilet seat and refusing to dry it. After this, he had an extremely poor work record. Prior to entering service, in 1941, he was forced to marry a girl he had impregnated. A short time after being in the Army, he began to have a sensation of "numbness in the feet as if walking on pillows," followed by feelings that his hands were severed from his body. "Everything looked strange to me, as if it was a mirage." About this time he also experienced spells of weakness and poor concentration. He was hospitalized several times during his military service because of these complaints, received insulin therapy for one month, and was finally discharged from service with the diagnosis of "psychopathy with possible schizophrenia." On discharge, his tremulousness and feelings of unreality persisted, and he was unable to work regularly. He became alcoholic, was restless, and complained of headaches, digestive upsets, and frightening nightmares. In 1946 and again the following year he was hospitalized for alcoholism. He was unable to hold a job for any length of time. He refused to take orders, being irritable and at times assaultive toward his superiors. In addition, his anxiety would become so great some days that he would require large amounts of alcohol and barbiturates to control it "and to keep from going berserk." For two years he maintained himself on this borderline adjustment, when, finally, his family prevailed upon him to seek psychiatric treatment. At the time of admission to this hospital, mental examination showed psychomotor retardation. Frequently, in the midst of a conversation he would stop talking and stare straight ahead for several minutes; at such times he was unresponsive to questioning, and he frequently required strong stimulation to be aroused from the state. He showed severe anxiety at all times, with sweating and palpitation. During his hospitalization he had periods of confusion, when he would wander off the ward and have no memory for where he had been. He continued to describe the sensation of "walking on clouds" and of "feeling funny," as though he were not all there. At times he spoke of seeing brightly colored balls in front of his eyes. He was frequently evasive when describing his symptoms, proclaiming that "certain people were out" for him, but admitting that he was not certain who they were.

CASE 2.—A white man aged 27 had a history of being a nail biter and of having temper tantrums as far back as he could remember. He had a belligerent attitude and a violent, explosive temper, so that at times he was dangerously assaultive. During his schooling period he had few friends, was truant frequently, disliked his teachers, and quit at an early age, ostensibly to go to work. His work record was sporadic and unsuccessful. In service his adjustment was poor. He would have periods in which he felt "shaky all over," especially when he became angry or when he was frightened by loud noises, such as thunder or subway trains. Besides drinking heavily, he was in frequent brawls. After his discharge from the service, his consumption of 2 or 3 qt. (2 or 3 liters) of beer daily continued because, he said, "of continuous nervousness and tremors." In addition, he complained of attacks of numbness of his arms and the back of his neck and sweating of his palms. He became irritable and insomniac and acquired various phobias,

4. Bleuler, E.: Textbook of Psychiatry, authorized English edition by A. A. Brill, New York, The Macmillan Company, 1924.

such as fear of crowds, closed places, cars and subways. Accompanying these complaints were periods of confusion and "black-outs"; he might wander the streets of New York for hours with no recall for what had transpired during the period. He became moody and withdrew from most of his social contacts. In an attempt to relieve the overwhelming anxiety, he turned to use of barbiturates and paraldehyde, to which he subsequently became strongly habituated. Although in reality his wife was unusually devoted to him, he became convinced she was unfaithful, accusing her of this in front of friends and relatives. Unable to hold a job, and with his marriage on the point of dissolution, he entered the hospital. Mental examination at the time of admission here showed him to be anxious and preoccupied, with markedly labile and frequently inappropriate affect. He believed that people on the outside were talking about him. He spoke of patients in the ward making derogatory remarks behind his back. While in the hospital he was withdrawn and stayed by himself a large part of the time.

Case 3.—A white man aged 27 gave a history of having lived in many foster homes and orphanages since an early age. Throughout his life he had always been hostile and sarcastic and had got along poorly with people. He attended school erratically and was truant frequently. On entering the service, he made an extremely unsatisfactory adjustment and presented a severe disciplinary problem, having been court-martialed several times. He was in an automobile accident while in the Army and was hospitalized six times with various somatic complaints having no relation to the trauma he had actually sustained. While in service, he was hospitalized in a neuropsychiatric ward because of "unconsciousness," which he stated occurred because of intense pain in his feet. Since being discharged, he had had six admissions to psychiatric services in hospitals. For the past six years he has complained of "black-outs," nervousness, and difficulty in walking. He had become habituated to the use of codeine and barbiturates. In addition, he had become convinced that "people had it in" for him. He had many somatic complaints, such as severe headaches, constipation, and sexual impotence. There developed flexion contractures of his toes, which were diagnosed as having a hysterical basis. Since his discharge from the service he had held numerous jobs, but none of these lasted more than a few days. His first admission to this hospital was to a surgical ward for epigastric pain; when he was reprimanded, with a threat of discipline, for numerous disturbances, he said he would jump out of a window. Mental examination at the time of admission to the psychiatric service showed him to be very anxious, circumstantial in his speech, and extremely evasive. He said he did not trust the physicians, who he thought were unfriendly to him. He said, "People are staring at me all the time. I can't take that crap." In the ward he was unfriendly, hostile, and suspicious, had no friends, and stayed by himself most of the day. He became intensely preoccupied with his somatic state, particularly his rectal and orthopedic problems. He offered to have his extremities amputated if that would help his difficulties.

Case 4.—A Negro aged 28 had been enuretic up to the age of 12 years. As a youngster, he would bite his lips when nervous. School adjustment was marked by frequent temper tantrums, truancy, and delinquency. He had always manifested unpredictable, impulsive behavior. His work history was poor and sporadic. In service he had advanced to the rank of sergeant, but, refusing to take orders, was court-martialed and, as a result, demoted to the rank of private. About this time he became extremely irritable and had insomnia, backache, headaches, and dizziness. He started to complain of "black-outs," in which he would lose track of his thoughts, so that he did not know what he was doing for periods up to several hours. In addition, he began to have inability to concentrate and to pay attention to his work. After his discharge from service (NP-Cdd), his adjustment continued to be poor. He began to drink excessively and withdrew from all his personal contacts. Two years before the present admission he received electroshock treatments for an agitated depression. Although his condition improved after these treatments, he did not feel well, and one day he became confused and found himself in Pittsburgh. He had complete amnesia for the intervening period of two days. The somatic complaints that had been present while he was in service persisted—pains in all parts of his body, lightheadedness, and feeling "strange." Sexual function, which had been good prior to service, had since that time deteriorated, so that the patient was unable to get an erection. It was due to the incapacitating effect of these various complaints that the patient finally sought treatment. Mental examination at the time of admission revealed him to be hostile, tense, and

suspicious. He was very anxious and repeatedly punched his right fist into his left hand, stating that if it was not for his mother he would never have come to the hospital. He was verbose and circumstantial. He told the examining psychiatrist that he did not trust doctors because of previous treatment he had had, which had not helped him, so that he felt the doctors were insincere. Numerous somatic complaints, many of an unusual nature ("my tongue's not in my mouth"), were noted. He spoke of being "picked on" by the attendants (most of whom, incidentally, were Negroes) because he was a Negro.

CASE 5.—A white man aged 25 was raised in a tough neighborhood in the Bronx. As a youngster he was belligerent and active in gang fighting. Although he was truant often, he graduated from high school, owing to family pressure. In service he was sent to five schools, was active socially, but did not study, so that he subsequently failed out of all of them. He felt that these failures were justified, for, as he said, "I had been wronged by Society by being flunked out of V-12; so what was the use after that?" He was classified as psychopathic by the Army and given a neuropsychiatric discharge. Since getting out of service, he had attended six colleges, none of them for more than a few months. He attempted to work part time but was unable to hold a job. During the years intervening between discharge from service and admission to the hospital, he received many months of group psychotherapy on an outpatient basis, receiving no benefit, however. In 1947 he had the sensation of "tension in his forehead," which consisted of "disturbing influences coming in and bothering him and keeping him confused. He became preoccupied with the fear that he might be attacked homosexually by strangers in the street. A sexual maladjustment became apparent, the patient having become completely impotent. Unable to continue with studies of any kind, and becoming increasingly disabled in the everyday activities of life he sought admission to the hospital. Mental examination at the time of admission revealed that he was constrained and anxious, and in tenuous contact with reality. He stared straight ahead, and speech was halting, disconnected, and at times irrelevant, so that it bordered on incoherence. His thinking was autistic, and he was preoccupied with his inability to adjust to life. "I have come upon some truths common to man. My make-up doesn't let me make them part of me. Influences prevent me from being good; I would like to deal with man as an emotional rational being but can't." He expressed feelings that his body was changing.

CASE 6.—A white man aged 30 stated that he never felt like a wanted child. In school he presented a disciplinary problem, did not get along with his fellows or teachers, and was truant frequently. He developed various sexual perversions at an early age. When he was 12 years old, he was sent to a reformatory for two years because of his part in a neighborhood disturbance. After getting out, he was arrested for stealing. He did not do well in service, drank heavily, was absent without leave, and was sentenced to two years in prison by the military authorities but was later pardoned. He continued to drink excessively after discharge and was unable to get along with his fellow employees or employers. He had become increasingly withdrawn and seclusive and was convinced that people were against him and had it in for him. He thought that people around him were talking about him and making fun of him. He committed impulsive acts, such as attempting to shoot his brother-in-law, attacking neighbors, and forging a signature to a check. During the past five years he had become increasingly withdrawn and seclusive. Mental examination at the time of admission revealed him to be extremely suspicious, with frequent blocking and somatic complaints. Affect was inappropriate to material discussed, and the patient showed impulsive and illogical thinking.

CASE 7.—A white man aged 24 had enuresis up to the age of 10. He did not do well in school and was a disciplinary problem; although he had an average intelligence quotient, at one time his parents had to place him in a school for retarded children. He recalled an unhappy home life because of frequent arguments between his parents. He was sent to a military school but was suspended when he assaulted a teacher. He made an inadequate adjustment in service and was given a neuropsychiatric discharge. On being discharged, he commenced to drink heavily. He attended several schools under the GI bill but always dropped out of them after a month or two because he "didn't like the work." Since 1945 he had expressed various somatic complaints, accompanied by feelings of depression. For this condition he took amphetamine, to which he became addicted. Two years before he had been bitten by a dog and feared that he might have contracted rabies. He received antirabies injections, and while receiving the shots he found it hard to swallow. He said he felt dizzy and "queer." He also began to feel that

"everything seemed far away and strange." He had become increasingly withdrawn up to the time of admission. Mental examination at the Veterans Administration Hospital revealed that the patient manifested frequent blocking, was apparently confused, and had that pronounced somatic preoccupation. Thinking was abrupt and frequently bizarre and illogical.

RESPONSE TO THERAPY

These patients were given various types of therapy in the psychiatric armamentarium: electric shock, narcosynthesis, insulin treatment (coma, subcoma, ambulatory), and intensive psychotherapy on an inpatient and an outpatient basis. During psychotherapy these patients produced minimal material, showed a marked dearth of ideas and associations, and apparently gained little insight. They had great difficulty in forming a relationship of any sort with the therapist. When therapy became difficult or productive of an unusual amount of anxiety, "acting-out," e. g., "eloping" from the hospital or outbursts of rage, was not uncommon. The extreme degree of anxiety present in these patients at all times seemed to show little diminution after many months of psychotherapy. The poor response to all the other therapies appar-

TABLE 1.—*Response to Therapy of Seven Schizophrenic Patients with Psychopathic Features*

	Cases						
	1	2	3	4	5*	6	7
No. of admissions to hospital	5	2	6	2	6	3	4
Total length of hospitalization, mo.	12	13	36	13	24+	15	23
No. of electroshocks	..	..	..	2	..	..	..
Insulin therapy							
Subcoma	10	30	..	6	24	..	..
Coma	..	17	..	10	16	..	..
Ambulatory	40	..	..	..	..	..	..
Narcosynthesis	+	+	+	+	+	+	+
Intensive psychotherapy (no. of mo.) (inpatient and outpatient)	12	13	48	13	12+	12	16

* Patient still receiving treatment.

ently indicated the refractoriness of this condition to the majority of readily available present-day techniques. All but one of the patients has since been discharged from the hospital; most patients were unimproved at the time of discharge. The types and amount of treatment each patient received are enumerated in Table 1.

COMMENT AND CONCLUSIONS

Bleuler [5] divided schizophrenic symptoms [6] into "fundamental" and "accessory" types. The fundamental symptoms (sometimes called primary, or basic) are those "which are present in every case and at every period of the illness." These symptoms are caused by disturbances of association, disorders of affectivity, and ambivalence. Among the more prominent manifestations of these are withdrawal and preoccupation, an autistic approach to life, marked dearth of ideas, stereotyped thinking, inappropriate affect, frequently out of harmony with the situation, pressure of

5. Bleuler, E.: Dementia Praecox or the Group of Schizophrenias, translated by J. Zinkin, New York, International Universities Press, Inc., 1950; footnote 4.

6. (*a*) Noyes,[2] (*b*) Bleuler,[5] (*c*) Polatin, P., and Hoch, P.: Diagnostic Evaluation of Early Schizophrenia, J. Nerv. & Ment. Dis. **105**:22, 1947. (*d*) Hoch, P., and Polatin, P.: Pseudoneurotic Forms of Schizophrenia, Psychiatric Quart. **23**:248-276, 1949.

thoughts, moodiness, and a confusing ambivalence in all relationships and activities (Table 2). These symptoms are the result of the patient's favoring fantasy over reality and his increasing tendency to withdraw from reality. Accessory symptoms (sometimes called secondary symptoms), according to Bleuler, are the evidence of emotional conflicts resulting from the schizophrenic patient's continuous inability to adjust, owing to the interference of the fundamental symptoms. Included with the latter are the more classic diagnostic symptoms, such as delusions and hallucinations. In respect to the necessity for the presence of accessory symptoms in

TABLE 2.—*Most Characteristic Symptoms of Schizophrenia with Psychopathic Features, with Differential Points*

Schizophrenic symptomatology [6]	Psychopathic symptomatology [8]
Fundamental (primary, basic) symptoms	Unreliability
A. Associational disturbances	Cruelty
Loss of continuity of associations	Cheating and dishonesty
Illogical or bizarre thinking	Bullying
Condensation of thoughts	Impulsive generosity
Stereotyped form of thinking	Bad judgment
Marked dearth of ideas	Inability to profit from experience
Blocking	Alcoholism
Pressure of thoughts	Selfishness
Magical thinking	Juvenile delinquency and difficulties with the law
Abrupt and incorrect thinking	Petty crimes
Inappropriate speech	Temper tantrums and enuresis
Preoccupation; withdrawal	Poor work history
Autistic thinking	Violent mood swings
Dereistic thinking	Lack of conscience
B. Affectivity disturbances	Sexual aberrations
Indifference—oversensitivity	Only verbal acceptance of social requirements
Inability to maintain a mood	Rejection of authority
Ideas lagging behind affect	Defective judgment
Moodiness	Nomadism
Inappropriate affect to emotional situations	Egocentricity
C. Ambivalence—diffuse and widespread	Emotional immaturity
D. "Pananxiety"—with neurotic and autonomic symptoms	Lack of insight; rationalizes readily
	Truancy; dislike of teachers
Accessory (secondary) symptoms	
Hallucinations	
Delusions	
Catatonic symptoms, etc.	

Differentiation of Schizophrenic Reaction with Psychopathic Features and True Psychopathy (Anethopathy) [8]

1. The schizophrenic with psychopathic features is not only antisocial but asocial as well, withdrawing from others; the true psychopath is definitely social.

2. The schizophrenic patient may be paranoid as a result of reactions conceived within; the so-called paranoid reactions in the true psychopath relate only to interference encountered in the immediate environment.

3. The schizophrenic's sexual life is limited; the true psychopath shows a very strong sexual drive and pressure.

patients before the diagnosis of schizophrenia can be made, Bleuler noted that "these can be completely lacking during certain periods or even throughout the entire course of the disease." Hence the diagnosis of schizophrenia should not, and cannot, be made solely on the absence or presence of the accessory symptoms, but should be based primarily on the presence of the more significant, and always present, primary (fundamental) ones. The latter symptoms when found, not singly, but as a constellation, show a "specific type of alteration of thinking, feeling, and relation to the external world" characteristic of schizophrenia, and of no other disease. The last point is of interest because the patients in this study (and it is

believed that they are characteristic of this group) show symptoms most closely related to the fundamental symptoms elucidated by Bleuler, the "accessory" type of symptoms being less often noted. When the latter were present in the series, they were usually in the form of paranoid ideation, ideas of reference, and hypochondriacal delusions.

> Because of the aforementioned psychotic difficulties, the patient becomes involved emotionally so that his judgment is warped; though he knows intellectually the difference between right and wrong, he cannot grasp it emotionally and in obedience to the demands of delusions, autistic thinking and emotional involvement, wrong may appear to him as right and right as wrong.[7]

Thus does the schizophrenic act psychopathically. The psychopathic symptoms of these patients (in addition to their schizophrenic difficulties) were those usually considered characteristic of the psychopathic state.[8] Among the most characteristic, as elucidated by Menninger,[8a] were complete unreliability, cruelty, cheating, bullying, impulsive generosity, bad judgment, inability to profit from experience, prominence of excessive drinking, and total disregard for truth, honesty, fairness, and justice. Other behavior disturbances apparent in the development of such patients were juvenile delinquency, petty crimes, truancy, temper tantrums, poor work history, and violent mood swings.[8b] The symptoms of these patients are not transient or episodic, but are definite and continuous for long periods. It is interesting to note that the schizophrenic process of these patients does not appear to progress or deteriorate rapidly with the appearance of accessory symptoms. Most of them are eventually discharged, rather than given chronic hospitalization. This is true in spite of our finding that these patients at best show only the minimal degree of improvement when exposed to most types of psychiatric treatments available, the majority of them showing, in fact, no improvement at all. This is well demonstrated by the fact that these patients are notoriously inadaptable to civilian life and usually have several rehospitalizations. The lack of response to treatment demonstrated in these patients seems to confirm the observation of Henderson and Gillespie[9] that "the inadequate, immature dispositional background of the psychopath may exercise a considerable influence prognostically in cases which symptomatically may be classified as psychotic." This influence is, apparently, to render the prognosis poor. This type of schizophrenia, as regards both its progress without treatment and its response to therapy, appears to resemble most closely the pseudoneurotic schizophrenia of Hoch and Polatin.[10] The patients in our series also tend to handle their overwhelming anxiety in a way similar to that of pseudoneurotic schizophrenic patients, namely, by developing vegetative dysfunctions and the entire gamut of neurotic symptoms, rather than overt psychotic manifestations.

7. Karpman, B.: Criteria for Knowing Right from Wrong: Attempt at Psychopathologic Interpretation of Criminal Responsibility and Guilt-Attitudes, J. Crim. Psychopath. **2**:376-386, 1941.

8. (*a*) Menninger, K. A.: Recognizing and Renaming "Psychopathic Personalities," Bull. Menninger Clin. **5**:150, 1941. (*b*) Karnosh, L. J., and Zucker, E. H.: A Handbook of Psychiatry, St. Louis, C. V. Mosby Company, 1945. (*c*) Lindner, R. M.: The Rorschach Test and the Diagnosis of Psychopathic Personality, J. Crim. Psychopath. **5**:69-93, 1943-44.

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SUMMARY

A study of a group of patients showing schizophrenia with psychopathic features is presented. It was found that these patients showed predominantly the "fundamental" symptoms characteristic of schizophrenia, and less often the "accessory" type of symptoms. Furthermore, these schizophrenic patients, with or without treatment, did not appear to deteriorate rapidly. Most of them were eventually discharged, only to return to the hospital because they were unable to adapt to the outside world. These patients received various types of therapy; electroshock, insulin coma, amobarbital-sodium interviews, and long-term intensive psychotherapy, on both an inpatient and an outpatient basis. Results were uniformly poor, the patients showing little or no improvement in every case. The presence of psychopathic symptoms in schizophrenia would thus seem to affect the prognosis adversely as regards abatement or remission of the process, with or without treatment. On the other hand, the utilization of a "psychopathic defense" by a schizophrenic person renders his prognosis unusually good as to the avoidance or slowness of future deterioration.

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PRIMARY MALIGNANT MELANOMA OF THE SPINAL CORD

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PRIMARY malignant melanoma of the central nervous system is a relatively rare neoplasm. Such a growth arising in the spinal cord is even more unusual. When one is encountered, it is often difficult to tell whether the lesion is secondary to a melanoma elsewhere in the body or whether it has spread from one in some other part of the central nervous system. Since many melanomas are not diagnosed until necropsy, it is sometimes difficult to ascertain just the point within the central nervous system from which the neoplasm arose, since the tumor frequently spreads throughout the subarachnoid space either by direct extension or by "seeding." Sometimes dense and extensive metastases occur throughout the leptomeninges, which have been described as "tumor meningitis." It was Virchow [1] who in 1859 first reported a case of primary melanoma sarcomatosis. Since that time occasional reports in the literature have appeared, but the number is still small.

Recently we have had the opportunity to study two cases of primary melanoma of the spinal cord in which the tumor was discovered early and operation was performed several months before death. This allowed a comparison of findings at operation with those at necropsy. In addition, one of the cases had some unusual features which, to our knowledge, had not been described previously.

REPORT OF CASES

CASE 1.—H. A. S. was first admitted to the Veterans Administration Hospital, Perry Point, Md., on Nov. 26, 1942, at the age of 53, because of mental disturbances. The diagnosis at that time was dementia praecox, simple type. The physical examination on admission showed nothing abnormal. The neurological examination disclosed only that the left pupil was slightly larger than the right and that a fine tremor of the tongue and of the extended fingers was present. The patient was under constant observation and made a good adjustment while in the institution. There were no complaints until December, 1948, when he spoke of vague pains in his abdomen. Apparently these were diffuse, and on Dec. 22 the urinary bladder was found

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1. Virchow, R.: Pigment und diffuse Melanose der Arachnoides, Virchows Arch. path. anat. **16**:180-182, 1859.

greatly distended; catheterization yielded 1,500 cc. of urine. Neurological examination at this time showed that the left pupil was still a little larger than the right, but both pupils reacted promptly to light and in accommodation. The reflexes of the arms were equal and active on the two sides. The knee jerk, however, was absent on the right and present on the left. Both ankle jerks were then absent, and there was an equivocal Babinski response on the left. The abdominal reflexes were not remarkable. A Naffziger test was done, and almost immediately the patient complained of severe pain in the upper lumbar region. On lumbar puncture, fluid was obtained which coagulated on standing and contained 740 mg. of protein per 100 cc., together with 4 lymphocytes per cubic millimeter. The Wassermann reaction was negative. It seemed clear that the patient had a Froin syndrome. Laboratory studies of the blood and urine gave results within normal limits. A roentgenogram of the spine taken on Jan. 7, 1949, failed to show any abnormalities. Because of the patient's mental status, detailed motor and sensory examinations could not be carried out. About one week after the onset of symptoms, a myelogram showed an irregular defect at the level of the 12th thoracic and 1st lumbar segments. Additional roentgenograms taken at this time showed a lesion in the pedicle of the first lumbar vertebra on the right side. Laminectomy from the 12th thoracic to the 2d lumbar vertebra was performed shortly after the myelogram was obtained. After the muscles had been removed from the lamina, a black, vascular tumor was observed extending between the laminas at the 12th thoracic and 1st lumbar vertebra and invading the pedicle on this side. As additional bone was removed, it was found that the tumor spread extradurally both up and down the spinal canal. When the dura was opened, the cord and upper roots of the cauda equina were found pushed posteriorly by a large black tumor. Much of the neoplasm was removed, but the operator could also see several small spots of black tumor tissue growing in the arachnoid elsewhere, as though the tumor was spreading by "seeding." After decompression of the cord, the edges of the dura were reapproximated, and the wound was closed in the usual manner.

The patient's course was one of steady deterioration. He became weak and irritable. Emaciation soon set in, and the course of his illness was marked by extreme anorexia. Many physical examinations throughout the course of illness failed to reveal a primary site for the melanoma. Death occurred on March 4, 1949, approximately four months after the onset of symptoms. Except for the lesions in the spinal cord, autopsy revealed no other abnormality. A melanoma was found involving the terminal portion of the spinal cord at the upper part of the cauda equina. The tumor measured about 2 cm. in length and 1.5 cm. in diameter, and it invaded the transverse process, as well as the body, of the 12th thoracic vertebra. The remainder of the spinal cord was normal. When the head was opened, small, dark-pigmented growths were seen scattered in the dura on the under surface of the brain just to the right of the midline. The rest of the brain appeared normal, as did the meninges. The optic nerves were not remarkable. The eyeballs were removed but were found to be normal.

Sections of the tumor disclosed cells of varying size which were arranged in nests and sheets. The nuclei were fusiform, with prominent nucleoli. Mitotic figures were numerous. Large amounts of intracellular and extracellular pigment were present. Stains for iron gave negative results, and it was later proved that the pigment was melanin. A primary source for the neoplasm outside the central nervous system could not be detected. The invasion of the surrounding laminae appeared to be by direct extension through the dura into the bone (Fig. 1).

CASE 2.—T. H., a white man aged 47, was admitted to the neurosurgical service of the Guthrie Clinic with a complaint of weakness of the left leg of two months' duration. The family and past histories were noncontributory. Several months before admission he became constipated without apparent cause, and about three months before admission his wife noted that his left leg jerked spontaneously while he was asleep. On both occasions a physician was consulted, but no cause was made out. About six weeks before admission the patient became aware that the left leg was weak and that his toe would catch on objects as he walked. Examination by his physician revealed that he had loss of pain sense over the leg. The weakness progressed steadily, so that at the time of admission he could barely get about with the use of a cane. The patient noticed spontaneously that heat from a hot-water bottle on the leg was not appreciated. Urinary frequency and dysuria developed a short while before he was seen in the clinic. There had been a loss of weight of about 15 lb. (6.8 kg.) during the past two

months, for which no explanation was offered. There were no symptoms indicative of intracranial pressure. He did not complain of pain, nor had he had any cough or gastrointestinal symptoms.

Physical examination disclosed nothing significant. Careful search for pigmented areas or black moles was unrewarded. Neurological examination, however, showed extensive changes. The patient was wide-awake, alert, intelligent, and cooperative, with no signs of aphasia. The cranial nerves were intact except for bilateral papilledema, of about 4 D. The veins were engorged and were no longer pulsating. No exudates or hemorrhages were seen. Muscular strength, tone, and dexterity of the arms and hands were normal. There was some weakness of the abdominal muscles, however, and Beevor's sign was present, with the umbilicus moving upward. In the right leg diffuse weakness of all muscle groups was present, although it was particularly severe in the quadriceps and the extensors of the thigh. The weakness of the left leg was more profound and generalized, and there was beginning muscular atrophy. Both

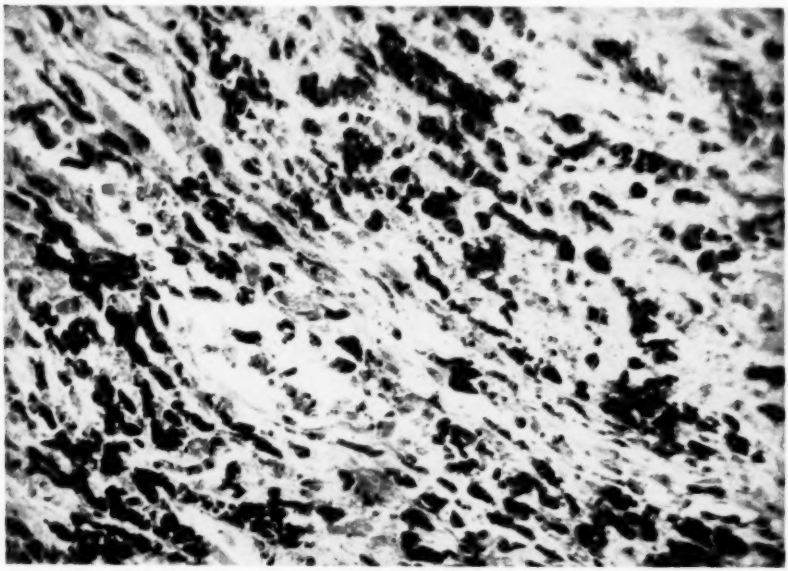

Fig. 1.—Microscopic view of the melanoma; × 420. Both intracellular and extracellular pigment can be seen. The structure resembles a sarcoma.

legs showed a decided decrease in muscular tone. No fibrillations or fasciculations were noted. Sensory examination revealed complete loss of pain and temperature sense bilaterally from the 10th thoracic segment downward. Touch sensibility was still present, but position sense was considerably diminished in both feet, and vibratory sense was absent below the xiphoid cartilage.

The tendon reflexes in the arms were not remarkable. The abdominal reflexes were absent, as were the cremasteric reflexes. The knee jerk was barely elicited on the left but was still present on the right. Both ankle jerks were surprisingly brisk. The plantar response was dorsiflexion on both sides. Ankle clonus was obtained without difficulty on the left but was sustained for only a few beats on the right. Laboratory studies, including blood studies, urinalysis, and serologic tests, gave normal results. Roentgenograms of the chest, the skull, and the spine failed to reveal any lesions.

Despite the presence of papilledema, a lumbar puncture was done, revealing a pressure of 300 mm. of fluid. The Queckenstedt test demonstrated a partial block, and the fluid withdrawn

was highly xanthochromic. It contained 2,400 mg. of protein per 100 cc., but only 4 cells per cubic millimeter. Cultures taken at this time, including that for Mycobacterium tuberculosis, were later reported as sterile.

In view of these findings, it was decided to investigate the intracranial contents. Bilateral carotid arteriograms were obtained. Excellent filming of the vascular tree was obtained on both sides, and no distortion was noted. Later, a ventriculogram was performed, which demonstrated moderate dilatation of the lateral and third ventricles. No air could be seen in the fourth ventricle, suggesting a tumor of the posterior fossa. A suboccipital craniotomy revealed marked and extensive arachnoiditis. The arachnoid was thick and milky in color. The cerebellar tonsils were bound tightly to the medulla, and the foramen of Magendie was completely occluded. This pronounced arachnoidal reaction extended down the cervical portion of the canal as far as could be seen. As already mentioned, the arachnoid had a milky color, and nowhere were to be seen any black or pigmented areas, which would suggest the spread of a melanoma or tumor meningitis. A small part of the vermis was then excised and an artificial opening made between the fourth ventricle and the cisterna cerebellomedullaris (cisterna magna). A catheter inserted into the aqueduct of Sylvius showed that it was apparently patent. Methylene blue instilled into a lateral ventricle soon appeared in the fourth ventricle, demonstrating the patency of the ventricular system.

Microscopic study of a biopsy specimen of the arachnoid showed a moderate amount of round-cell infiltration with prominent fibroblastic changes, all suggestive of an inflammatory reaction. There was no evidence of neoplastic cells. The postoperative course was benign. Several days later methylene blue was again placed in the lateral ventricles. On lumbar puncture, the dye could not be recovered in the lumbar region. Again xanthochromic fluid was obtained, and the Queckenstedt test then revealed a spinal block. Two days later Naffziger's sign was elicited. This was the first occasion on which the patient complained of pain in the back.

Ten days after the craniotomy a myelogram demonstrated a complete block at the first lumbar segment. The contours described by the ethyl iodophenylundecylate (pantopaque*) suggested an intramedullary neoplasm. It was during this procedure that we encountered a most remarkable spinal fluid. It was coal black. It contained a large amount of material which clotted within a few minutes and which, on removal from the rest of the fluid, was deep red. The color of this fluid made it seem certain that the tumor was a melanoma and was the first indication of the possible histological nature of the disease. Again, the patient was examined in an effort to find any cutaneous or retinal lesion, but none could be found.

A laminectomy revealed no evidence of erosion of the pedicles or of the vertebral bodies. The dura appeared intact, but it had a blackish color, which after the dura had been opened was found to be due to a dense black neoplasm lying within the dura, but not actually invading it. The conus and the cauda equina were bound by a mass of black material having the consistency and color of tar. The mass surrounded the spinal cord on all sides but was almost exclusively beneath the arachnoid. Much of this material was removed from about the conus, which was swollen. The conus was incised longitudinally, and it was found that the neural tissue was only 2 mm. in thickness and that the inside of the conus was filled with the neoplasm, which could gradually be shelled out and did not appear to invade the substance of the spinal cord. A capsule was not seen, however, and it was found that the tumor had penetrated the cord on the anterior surface. At the time of operation, we observed many small nodules lying along the cauda equina and a few on the surface of the spinal cord up to about the tenth thoracic segment. The arachnoid was stained black, and the color could be wiped off, so that it was thought to be due to the spinal fluid, which also was black. Above the 10th thoracic segment we could see evidences of arachnoiditis.

After operation the patient was completely paraplegic, and the course of his illness was steadily downhill. The suboccipital area of decompression remained soft, and the Naffziger sign disappeared. The papilledema disappeared, and throughout the final stage of the illness he showed no signs of intracranial pressure. Several lumbar punctures were done during this period. At times they showed a partial block; at other times, a complete block. The fluid remained xanthochromic, and at no time was the spinal fluid protein above 126 mg. per 100 cc. Until the time of his death, six months after the laminectomy, there were no new neurological signs. The sensory and motor level persisted at about the 11th thoracic level. An automatic bladder could not be

formed, and he remained incontinent. There was steady loss of weight. Clinical evidence of metastasis could not be detected, and several roentgenograms of the chest were taken, all of which appeared clear. Shortly before the final episode there developed fever and pain in the flanks, which was thought to be due to pyelonephritis, and within a few days the patient died.

Necropsy disclosed a remarkable picture. The neoplasm had recurred and was then many times as large as it was at operation. Numerous tumor nodules were scattered throughout the cauda equina and over the surface of the cord (Fig. 2). Some had spread up into the intracranial cavity, where they were all small, many of them no larger than a pinhead, and scattered along the

Fig. 2.—Site of the tumor and cauda equina as seen at autopsy, several months after operation. The large amount of black pigment is obvious.

arachnoid, over the base of the brain, and along the cranial nerves. Several were noted around the sella turcica. None were found over the cerebellum or the cerebral cortex. Invasion of the tumor along the nerve roots in the lumbar and sacral regions was noted, and extension for several centimeters along the course of the main nerve trunks was visible on gross inspection. No evidence of tumor tissue outside the central nervous system was detected. The neoplasm seemed to be confined entirely within the meninges, and almost exclusively within the spinal cord.

The sections of the tumor, both grossly and microscopically, resembled the ordinary malignant melanoma. The tissue was friable and dark brown to black. Microscopically, large sheets of oval cells, with prominent round or oval, dark-staining nuclei, were present. Numerous large and small blood vessels ran throughout the neoplasm. Frequently the cells were arranged in

whorls or massed around such blood vessels. Many of the cells contained brown pigment, which did not stain for iron. Masses of black extracellular pigment were scattered at random throughout (Figs. 3 and 4). Several of the pigment-bearing cells contained small nuclei, while others contained three or four nuclei and were typical giant cells. Mitotic figures were prominent in all sections. When the brain was cut, tiny dark areas were seen in the ependyma of all the ventricles; these areas looked as though pepper had ben sprinkled on the surface. No tumor metastases were seen within the substance of the brain.

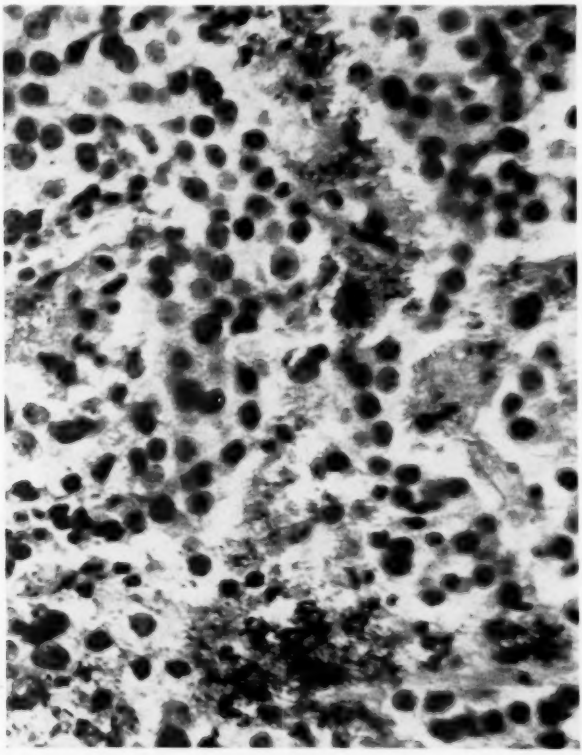

Fig. 3.—Microscopic view of the tumor removed at operation showing the distribution of melanin; × 420. Neoplasm resembles a carcinoma.

In the first case described the typical features of a spinal-cord tumor of rapid growth and invasive powers were presented. It is noteworthy that pain, a frequent complaint of patients with such tumors, was absent. The neoplasm rapidly penetrated the dura and caused bony destruction within a relatively short time after the onset of symptoms. Survival after the operation was limited to three months, although mental factors may have contributed to the final outcome. Careful postmortem studies failed to reveal neoplastic tissue elsewhere in the body except in the region of the lower thoracic portion of the spinal cord and the bones immediately adjacent thereto.

The second case had many unique features. First, there was the presence of black spinal fluid indicating that at least once during the course of the illness there was free melanin in the spinal fluid. Since many lumbar punctures were performed, both before and after operation, we can assume that melanin was freed only at intervals, since at other times the fluid was xanthochromic and in no way differed from that seen in cases of ordinary spinal-cord tumors. Another feature was the extreme arachnoidal reaction, which was observed at the first operation. The patient had typical signs of massive adhesive chronic arachnoiditis. This process

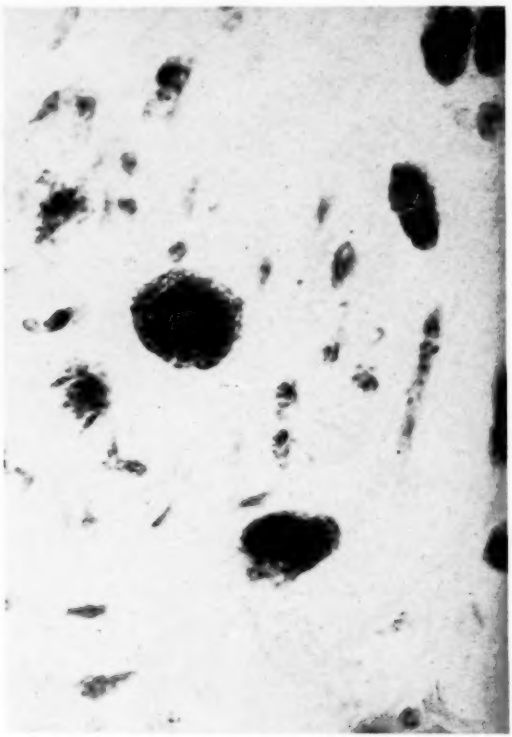

Fig. 4.—Photograph showing the detail of pigment distribution; oil immersion; × 940.

was so marked in the region of the foramen of Magendie that occlusion of the ventricular system resulted and secondary hydrocephalus developed. The condition was relieved by the creation of an artificial stoma. It is our belief that the arachnoiditis was the result of a chemical meningitis due to free melanin, and that at this stage it was not a "tumor meningitis." The tumor in the second case did not have quite the invasive powers noted in the first case and did not extend beyond the dura, although it did circulate freely in the spinal fluid, seeding over the entire surface of the brain, particularly along the base of the temporal and frontal lobes,

as well as on the ependyma of the ventricular system. Heavy deposits were noted along the entire length of the cauda equina, and the tumor extended down the nerves as far as the posterior root ganglia. The situation found at necropsy was quite different from that seen at operation. Arachnoiditis was the outstanding finding at operation, whereas later there were seeding and a real "tumor meningitis" over the entire cord and the base of the brain.

COMMENT

Primary malignant melanomas of the central nervous system have always been uncommon neoplasms, while those arising within the spinal cord are rare. Rasmussen, Kernohan, and Adson [2] stated that 0.5% of all spinal-cord tumors were melanomas and that they constituted about 5% of the intramedullary neoplasms, but the authors failed to state whether they were primary or secondary.

The origin of these tumors is an unsettled point, and at present there are several theories which offer partial explanations. Small pigmented areas in the pia, around the brain stem and the cervical portion of the cord, were noticed in routine autopsies many years ago. Farnell and Globus [3] described this finding as normal in infants. Microscopic study of these areas show connective tissue containing chromatophores. Even the origin of the melanomas elsewhere in the body is still under discussion. Masson [4] and his followers have held to the nerve-tissue origin of dermal melanomas. Ewing [5] stated the opinion that superficial melanomas arise from the Merkel-Ranvier cells, whereas the deep ones stem from the Wagner-Meissner corpuscles. The latter structures are present in the meninges, and, as Strong [6] pointed out, could be a source of the melanoma. Ribbert [7] believed that the melanoma developed from specific mesoblastic cells which are found in early embryos and are unrelated to other types of cells. At present, most authors are of the opinion that the pigment is derived from a melanoblast which is in some way connected with the nervous system. These cells then exude the pigment, which is picked up by other cells, described as chromatophores, although Kessler [8] believes that this occurs only when the melanoblasts become malignant. Allen [9] has recently proposed the epidermal origin of melanomas, being of the opinion that epidermal cells undergo change and develop into pigment-producing cells. He does not suggest how melanomas in the central nervous system originate. Another explanation is that "cell rests" within the nervous system contain cells with the ability

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3. Farnell, F. J., and Globus, J. H.: Primary Melanoblastosis of the Leptomeninges and Brain, Arch. Neurol. & Psychiat. **25**:803-823, 1931.

4. Masson, P.: Pigment Cells in Man, in Biology of Melanomas, Special Publications, New York Academy of Sciences, No. 4, 1948, pp. 15-47.

5. Ewing, J.: Problems of Melanoma, Brit. M. J. **2**:852-856, 1930.

6. Strong, R. M.: Primary Melanoblastoma of the Cerebellar Leptomeninges with Widespread Extracranial Metastasis, Arch. Path. **44**:477-484, 1947.

7. Ribbert, cited by Ewing, J.: Neoplastic Diseases, Ed. 3, Philadelphia, W. B. Saunders Company, 1920.

8. Kessler, M. M.: Melanoblastosis and Melanoblastoma: Primary and Secondary Involvment of the Brain, Am. J. Cancer **30**:19-31, 1937.

9. Allen, A. C.: A Re-Orientation on the Histogenesis and Clinical Significance of Cutaneous Nevi and Melanomas, Cancer **2**:28-58, 1949.

to produce melanin and that under certain circumstances these cells become malignant. Since the brain and spinal cord originally developed from the ectodermal layer of the embryo, it is possible that some of these primary cells do remain, but the process that causes them to become malignant is obscure.

Diffuse infiltration of the leptomeninges over the surface of the spinal cord and brain has been described by several authors. Bakody and associates [10] stressed the term "tumor meningitis." They pointed out that the leptomeninges are separate from the subdural space and that the tumor cells spread throughout the subarachnoid space but do not involve the dura. In our cases, not only the meninges, but also the ependyma, was infiltrated.

The majority of the recorded melanomas have not spread outside the central nervous system, although there have been exceptions, as reported by Strong.[9] One would gather that the melanomas in the central nervous system are less malignant than those arising outside the central nervous system, which usually run an extremely rapid course with widespread metastases. Why melanomas of the central nervous system do not erode blood vessels and metastasize outside the brain and spinal cord is not clear.

The histological picture of melanomas within the central nervous system shows considerable variation. Some melanomas resemble carcinoma; others, sarcoma. The cells present great differences in size and shape. They may be present in sheets or whorls or clumped around blood vessels. In a study of serial sections, many different histological pictures may be seen within the same tumor. Some areas resemble benign meningiomas, while others look not unlike a spindle-cell sarcoma. Pigment is found both in the cells of the neoplasm and lying free between the malignant cells. It can be analyzed directly for melanin, or the dihydroxyphenylalanine test for melanoblasts reaction may be utilized. In this test a chemical agent produces a black substance when it reacts with the enzyme melanogenase, indicating the presence of cells that are producing melanin.

Winkelman and associates [11] laid down the principles for diagnosis of primary melanomas, in which they stressed that a primary neoplasm elsewhere could not be found and that the patient had a diffuse melanoblastic infiltration of the pia-arachnoid. This is the late situation, seen post mortem, but during the early stages, particularly with the spinal-cord melanomas, the symptoms may be simply those of a mass and it is not until months later that the widespread meningeal spread occurs.

Examination of the spinal fluid is also very helpful if melanoma cells are seen in the sediment or if the fluid contains free melanin. Apparently, the latter circumstance has been very infrequent, although Wortis and Wortis [12] have found it in some of their cases. An increase in protein content and xanthochromia indicate only a block and do not give any information concerning the specific type of neoplasm. At operation, the only possibility of confusion is with hematoma. Some

10. Bakody, J. T.; Hazard, J. B., and Gardner, W. J.: Pigmented Tumors of the Central Nervous System, Cleveland Clin. Quart. **17**:89-101, 1950.

11. Winkelman, N. W.; Gotten, N., and Silverstein, A.: Primary Melanoblastosis of the Meninges, Arch. Neurol. & Psychiat. **35**:919-920, 1936.

12. Wortis, H., and Wortis, B.: Metastatic Melanomas Involving the Central Nervous System, Arch. Neurol. & Psychiat. **36**:601-611, 1936.

hematomas take on a black appearance, which may be difficult to differentiate grossly from that of a melanoma. A frozen section, however, will promptly clear up the doubt.

Treatment of these lesions is still far from adequate. If the tumor is small enough that it can be removed completely, a cure may be obtained. Tumors within the central nervous system appear to have a relatively low grade of malignancy, but, in view of their tendency to spread via the spinal fluid, it is unlikely that they will be recognized early enough. In most cases only palliative measures can be carried out. In Case 2 the formation of a new foramen of Magendie relieved the hydrocephalus and preserved the patient's vision for the remainder of his life. The attack on the primary lesion made him worse, if anything. Certainly, to leave the dura open and attempt to decompress the cord is of no particular benefit. X-ray therapy has proved a failure. As yet, there are no chemicals or hormones which are satisfactory in causing a melanoma to regress.

Several atypical pigmented tumors within the central nervous system have been described by Bakody and associates [10] and by Ray and Foot.[13] The latter authors described meningiomas that contained pigmented cells. These behaved like benign lesions, and the patients lived for many years after operation. The relationship of this type of neoplasm to the ordinary malignant melanoma is not clear.

There seems to be no clear-cut clinical picture which will allow a preoperative diagnosis. The presence of multiple and rapidly extending lesions may arouse suspicion of a melanoma. However, detailed laboratory studies in which free melanin or melanin-containing cells are found in the cerebrospinal fluid are necessary to establish such a diagnosis. From the recorded case histories, this has not been usual. Rarely, melanin has been found in the urine, the presence of which may lead to the discovery of a melanoma in the central nervous system.

SUMMARY

Two cases of malignant melanoma arising within the spinal cord are reported. Detailed necropsies failed to disclose an origin outside the central nervous system. In both cases "seeding" of tumor cells throughout the subarachnoid space, amounting to "tumor meningitis," had occurred. In the second case the cerebrospinal fluid contained so much free melanin that it was black. It is suggested that such an occurrence may have been responsible for the arachnoiditis, which later produced increased intracranial pressure.

The origin of melanoma within the central nervous system is briefly discussed. Treatment of this neoplasm has been unsatisfactory.

13. Ray, B. S., and Foot, N. C.: Primary Melanotic Tumors of the Meninges, Resemblance to Meningiomas, Arch. Neurol. & Psychiat. **44**:104-117, 1940.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

INFLUENCE OF LOW FAT DIET ON BLOOD LIPID LEVELS IN HEALTH AND MULTIPLE SCLEROSIS. V. A. WILMOT and R. L. SWANK, Am. J. M. Sc. **223**:25 (Jan.) 1952.

Wilmot and Swank found that the average values and range of values of various plasma lipid fractions for normal subjects and for patients with multiple sclerosis were approximately the same. On a low-fat diet the phospholipid and cholesterol levels of the blood decreased equally in the two groups, but there was no definite sequence of lipid-level reduction in either group. The total lipids of cellular components of the blood were the same in the two groups and were not affected by a low-fat diet.

BERLIN, New York.

C^{14}-CHOLESTEROL: II. OXIDATION OF CARBONS 4 AND 26 TO CARBON DIOXIDE BY THE INTACT RAT. I. L. CHAIKOFF, AND OTHERS, J. Biol. Chem. **194**:413,1952.

The conversion of cholesterol-4-C^{14} and cholesterol-26-C^{14} to carbon dioxide was studied in the rat. A pronounced difference in the extent of oxidation of these two carbons to carbon dioxide was observed. As much as 31% of the chain carbon was eliminated as carbon dioxide in expired air in 24 hours. Under similar experimental conditions, none of the ring carbon appeared as carbon dioxide. Intestinal bacteria play a minor role, if any, in this oxidation of cholesterol to carbon dioxide.

PAGE, Cleveland.

DISTRIBUTION OF TRANSAMINASES IN RAT ORGANS. J. AWAPARA and B. SEALE, J. Biol. Chem. **194**:497, 1952.

The transaminase activity of rat brain was measured in terms of glutamic acid formed. The results in other organs point to the existence of multiple transaminating activities. γ-Ketoglutaric acid appears to be the most important keto acid involved in the reaction. Of all free amino acids, glutamic acid exists in highest concentrations in the eight organs examined.

PAGE, Cleveland.

HOMEOSTATIC STUDIES IN PATIENTS WITH SO-CALLED PSYCHOSOMATIC DISEASE: PEPTIC ULCER. C. RUPP, H. E. RIGGS, R. S. BOLES, and P. S. SHORE, J. Nerv. & Ment. Dis. **114**:384 (Nov.) 1951.

To determine the ability of patients with a psychosomatic disorder to maintain homeostatic equilibrium, the investigators subjected 40 men with quiescent peptic ulcer to the cold pressor test at weekly intervals throughout a year. Their reactions were more variable and showed more marked individual differences than did those of a normal group. Reactions within normal limits were found consistently in only half the group.

BERLIN, New York.

PERFORMANCE OF COMPLEX VISUAL TASKS AFTER CEREBRAL LESIONS. H. TEUBER, W. S. BATTERSBY, and M. B. BENDER, J. Nerv. & Ment. Dis. **114**:413 (Nov.) 1951.

Tests of complex perceptual discriminations administered to men with focal brain injuries indicate that the performance of the parieto-occipital group is poorer than that of the group with frontal injuries. However, the deficits are not specific for lesions of the frontal or the posterior lobe.

BERLIN, New York.

PULSATILE ACTIVITY OF CELLS FROM THE HUMAN BRAIN IN TISSUE CULTURE. C. T. POMERAT, J. Nerv. & Ment. Dis. **114**:430, 1951.

Pulsatile activity of non-neoplastic human oligodendrocytes was studied by the method of tissue culture. The material was obtained mostly from the cortex of patients with psychiatric disease. The material was recorded by means of the time-lapse cinematographic technique. Pulsations of oligodendrocytes were found at the rate of 8 to 23 per minute. In adult cat tissue, there are indications that pulsatile oligodendrocytes may exist in the peripheral nervous system.

BERLIN, New York.

ELECTROMYOGRAPHIC OBSERVATIONS ON THE POSTOPERATIVE DISC PATIENT. E. W. MACK, J. Neurosurg. **8**:469 (Sept.) 1951.

Electromyographic studies of the sacrospinalis muscles in patients complaining of low-back pain following the operative removal of a herniated intervertebral disk in the lumbar region have yielded evidence of segmental denervation. Mack has studied electromyographically 18 cases of postoperative back pain, including 6 cases of sacrospinalis denervation associated with severe lower-back pain.

Evidence of reinnervation of the previously denervated muscle groups was observed 148, 230, 115, and 293 days after operation. In all cases the improvement or cessation of pain paralleled the improvement in the electromyographic recordings, indicating a return of innervation to the involved muscle segments.

Mack calls attention to the likelihood of a stretch injury of the posterior division of the spinal nerve root being a cause for this denervation. There is also a probability of a localized denervation occurring on an ischemic-block basis, produced by the rise of self-retaining retractors.

ALPERS, Philadelphia.

DAILY FLUCTUATIONS OF MAGNESIUM IN RELATION TO THE RHYTHM OF SLEEP. A. RUBINO and R. BALBI, Acta neurol. **6**:618, 1951.

Rubino and Balbi examined the fate of magnesium in the blood of 25 subjects. There was a progressive increase in the amount of this element from morning to night hours. The largest amount was found early in the morning when the subjects awoke. Rubino and Balbi believe that magnesium ions play a fundamental role in regulating the sleep rhythm.

ARIETI, New York.

PATHOPHYSIOLOGY OF MUSCULAR CRAMPS. T. ALAJOUANINE, J. LEFEBVRE, and J. SCHERRER, Rev. neurol. **81**:633 (Aug.) 1949.

The authors demonstrate that intra-arterial injection of neostigmine into a vessel supplying muscles already fasciculating from neurological disease will produce cramps in the affected muscles. They note the appearance of spontaneous cramping in various neurological diseases, particularly those involving the motor system, and the frequent association of cramps with fasciculations. Electromyographic study of muscle cramp reveals strikingly regular electrical activity of the motor-unit type. The authors believe that on the basis of these observations it is probable that the site of disturbance which initiates the cramp is at the motor end-plate. They note that this is the site of the action of neostigmine, which facilitates cramp. They believe that antidromic impulses possibly are responsible for the maintenance of the cramp. Another mechanism responsible may be the greater sensitivity of denervated muscles to neurohumoral substances.

LEGAULT, Washington, D. C.

INFLUENCE OF DIRECT STIMULATION OF HYPOTHALAMUS ON DEPRESSOR REFLEX OF THE CAROTID SINUS. F. BRAUNER, F. BRÜCKE, and F. KAINDL, Wien. klin. Wchnschr. **61**:676 (Oct. 21) 1949.

Both carotid arteries were exposed in two dogs, and the carotid sinus on one side was stripped of its nerve supply, the sinus on the other side being isolated by ligation of all the carotid branches cephalad to it. In the unnarcotized animal a fall of blood pressure of about 40 mm

Hg and an increase in respiratory amplitude and frequency could readily be obtained through direct stimulation of the sinus. Four other dogs with similarly exposed carotid sinuses were trephined under chloral hydrate anesthesia and electrodes introduced into the hypothalamus. The records showed that the blood pressure increased upon thalamic stimulation alone and that the respirations were shallow and slow. Upon increase of pressure within the sinus, the blood pressure fell about 40 mm. Hg, with the presence of slight bradycardia. Elimination of the thalamic stimulus at this point diminished the pressure by another 50 mm. Hg. The conclusion is reached that sympathetic reflex may be synergic with the depressor action of epinephrine.

MASON, New York.

Neuropathology

HYSTERICAL PARALYSIS ASSOCIATED WITH POLIOMYELITIS. R. H. YOUNG and H. T. HERMANN, J. A. M. A. **147**:1132 (Nov. 17) 1951.

Young and Hermann report a case of poliomyelitis with associated hysterical paralysis and sensory disturbances in a woman aged 22. The illness started with headache, fever, nausea, and vomiting. On the third day there was a decided reduction of sensation to pain and touch over the entire left side of the body, and the patient was sent to the hospital.

Neurologic examination showed the cranial nerves to be normal except for absence of the gag reflex. There was no facial asymmetry, and the optic fundi were normal. The motor status showed a moderate degree of diffuse weakness in the left arm and leg, which was more pronounced peripherally. The deep reflexes were present and equal in the upper and lower extremities on the two sides, and the superficial reflexes were normal. Sensory tests showed a moderate degree of hypalgesia and hypesthesia, which extended over the left side of the body.

A lumbar puncture on the fourth day of illness showed a normal pressure of 130 mm. of water. The cell count was 62 per cubic millimeter, with 56 lymphocytes.

A diagnosis of poliomyelitis was made. During the early part of her hospital stay there was little change in her general condition, but the degree of paralysis became somewhat less and the sensory loss was somewhat variable and became less marked.

The patient was tense and irritable and at first would not discuss her emotional tension. As she improved, she revealed the presence of marital disharmony, due to her involvement in an extramarital affair and culminating in a suicide attempt by the husband. He had returned home from the hospital only the week before the wife's present illness began.

On the fifth day of hospitalization the spinal fluid showed normal pressure, with a cell count of 16 per cubic millimeter and a total protein content of 38 mg. per 100 cc. At this time she was given some explanation of the hysterical mechanism and was encouraged to get out of bed. She was able to get around well, although the diminution in sensation over the left side of the body remained until the time of her discharge from the hospital.

This case is of some significance in that it emphasizes the fact that there are many emotional repercussions in poliomyelitis and that on occasion the illness may be utilized in a hysterical conversion.

ALPERS, Philadelphia.

ACUTE HEMORRHAGIC LEUCOENCEPHALITIS. J. MACARDLE, L. VAN BOGAERT and F. LHERMITTE, Rev. neurol. **81**:709 (Sept.) 1949.

The authors report two cases of acute hemorrhagic leucoencephalitis, with pathologic study, first described by Hurst in 1941. Stupor, of rapid onset, is followed by coma, hyperthermia, and, occasionally, hemiplegia and convulsions. The lesions, found predominantly in the white matter of the cerebral hemispheres, consist of dense perivascular infiltrations of leucocytes, fibrinous exudates, and petechial hemorrhages. The parenchyma itself shows only slight changes.

This leucoencephalitis is clearly distinguishable from brain purpura due to other causes and from other forms of so-called "hemorrhagic encephalitis" in that it is a true encephalitis. In their distribution the lesions resemble perivenous encephalitis (postinfectious, etc.), but the histopathologic picture differs.

LEGAULT, Washington, D. C.

HIGH LIPID CONTENT OF SPINAL FLUID IN CASE OF NEUROMYELITIS OPTICA. M. JANBON, L. BERTRAND, and P. IZARN, Rev. neurol. **81**:740 (Sept.) 1949.

In a patient with subacute neuromyelitis optica who died within four months, of trophic complications, the spinal fluid was amber and highly refractile, due to its high fat content (500 mg. per 100 cc.). This high content was first discovered when the process was already waning.

The authors stress the diagnostic value and the significance of the high-fat content of the spinal fluid, which is concomitant with the massive demyelination of the spinal cord. It is transitory and disappears at the same time that the spinal fluid becomes normal in color and cell count. They are of the opinion that the association proves that demyelination is the fundamental process of the condition.

They theorize concerning the cause of neuromyelitis optica. Inoculation of rabbits with the spinal fluid failed to produce the disease. They note the occurrence, four years before onset of the disease, of undiagnosed generalized erythema, and a short time before onset, of an infected cut on the leg.

LEGAULT, Washington, D. C.

Psychiatry and Psychopathology

THIOCYANATE PSYCHOSIS. H. J. M. BARNETT, M. V. JACKSON and W. B. SPAULDING, J. A. M. A. **147**:1554 (Dec. 15) 1951.

A series of eight cases of thiocyanate psychosis presenting problems in the diagnosis of confusional psychosis is presented. Two of the patients died. In no instance was serum-cyanate measurement used to guide administration of the drug.

Barnett and his co-workers emphasize several difficulties that hinder the prompt recognition of thiocyanate psychosis. Clinically, the toxic delirium varies from mildly stuporous, confusional states to delusional, hallucinatory, or maniacal outbursts. The psychosis resembles, and may coexist with, bromide psychosis. The onset of mild confusion may complicate the problem, since the patient may then unwittingly further overdose himself. The fact that the psychosis is increasing in severity and the drug is known to have been discontinued does not invalidate the diagnosis. Focal neurological signs should not be allowed to confuse the diagnosis. In at least four of these cases the physicians considered the patient to be suffering from cerebral vascular disorders or "hypertensive encephalopathy."

ALPERS, Philadelphia.

ACUTE INTERMITTENT PORPHYRIA: ASSOCIATED PSYCHIATRIC SYMPTOMS TREATED BY ELECTROSHOCK. J. G. FREEMAN and L. C. KOLB, Proc. Staff Meet., Mayo Clin. **26**:401 (Oct. 24) 1951.

Porphyria presents symptoms in two distinct groups: (1) chronic congenital porphyria, in which cutaneous phenomena dominate, and (2) acute toxic or acute idiopathic types, in which the chief symptoms are referable to the nervous system and gastrointestinal tract.

About 350 cases of porphyria have been reported in the literature. Only one paper, that by Levy and Perry, reports a case in which the mental manifestations were of primary importance. The clinical picture in their case was characterized by several psychotic episodes, preceded a few days by mild gastrointestinal disturbances and the excretion of dark-red urine. Pentylene tetrazol U.S.P. (metrazol®) shock therapy and electroshock therapy had only slight temporary effect upon the course of the psychotic reactions.

Freeman and Kolb describe a case of porphyria in a woman of 40 which was also presented primarily as a mental disturbance. There was a history of 11 years of intermittent pain in the right upper abdominal quadrant, followed by an acute attack characterized by a psychotic reaction, schizophrenic in type. This was manifested by the patient's marked social withdrawal, periods of muteness, refusal to eat, regressive behavior with incontinence and smearing of dejecta, delusions, and hallucinations. This psychotic state persisted after the excretion of porphyrins in the urine ceased. No neurologic or physical sequelae occurred, although the patient complained of paresthesias in the distal portions of the extremities when she became responsive.

Since there was no change in the behavior disturbance after the qualitative reactions for urinary porphyrins became negative, a total of six electroshock treatments were given. After the

fourth treatment the patient was oriented. After the sixth treatment her emotional and behavior state was essentially normal for her, and she was discharged. There was no objective clinical evidence of involvement of the central or peripheral nervous system, although the patient did present, in her paresthesias, subjective symptoms suggesting such a disturbance.

In discussing the fact that this patient responded to shock therapy, whereas that of Levy and Perry did not, the authors raise the questions whether the condition of patients with porphyria is refractory to electroshock therapy during the course of the acute metabolic disturbance or whether electroshock therapy itself can affect the porphyric disturbance.

ALPERS, Philadelphia.

Meninges and Blood Vessels

SALMONELLA MENINGITIS. M. L. BEENE, A. E. HANSEN, and MACD. FULTON, A. M. A. Am. J. Dis. Child. **82**:567 (Nov.) 1951.

Henderson, in 1948, described the occurrence of Salmonella meningitis in three infants and in a review of the literature to that date was able to collect 144 instances of this type of infection in human subjects. In his series, death resulted in 128 of the 147 patients, a mortality rate of 87.5%.

The present authors describe the first recorded case of meningitis due to Salmonella sp. (Type Montevideo), occurring in a 7-week-old boy. It was not until one month after the infant's admission to the hospital that grossly purulent fluid obtained from the right lateral ventricle was cultured and revealed the causative organism to be a Salmonella, later identified as Type Montevideo. Sensitivity tests revealed chloramphenicol to be most effective, and this was administered instead of the previously given sulfadiazine and streptomycin. However, by this time hydrocephalus had developed, and, in spite of general improvement, the child was sent home six weeks later with a final diagnosis of (1) meningitis due to Salmonella sp. (Type Montevideo) with recovery, (2) hydrocephalus secondary to meningitis, and (3) mental retardation secondary to meningitis.

A review of the recent literature on Salmonella meningitis contains 87 cases, of which 72 were fatal, a mortality rate of 82.7%. It is thus seen that there has been no significant reduction in the fatality rate during the present use of antibiotics. However, some recoveries have been recorded with the use of both sulfonamides and antibiotics, and early diagnosis of the infection and adequate treatment are urged to prevent neurologic complications, such as occurred in the case here presented.

ALPERS, Philadelphia.

COCCIDIOIDAL MENINGITIS: REPORT OF FOUR CASES WITH NECROPSY FINDINGS IN THREE CASES. V. E. JENKINS, and J. C. POSTLEWAITE, Ann. Int. Med. **35**:1068, 1951.

Four cases of coccidioidal meningitis are reported, with necropsy observations in three of the cases.

In the first case a cavitary pulmonary lesion developed while the patient was in Arizona; this was followed three years later by coccidioidal meningitis. The results of serologic studies for coccidioidal infection were compatible with a disseminated form of the disease.

For many months he was critically ill and failed to respond to streptomycin, penicillin, and potassium iodide therapy. He was given the antibiotic actidione intravenously, after which he showed a delayed, but remarkable, clinical response and was alive three years after he was first found to have meningitis. This response is interpreted as a remission, rather than a complete recovery, however, since the spinal-fluid examination seven months after treatment still showed pleocytosis, increased protein, and a low sugar content.

In the second case meningitis developed while the patient was stationed at Camp Roberts, Calif., and there years later the meningitis was still present as an active infection. Therapy for 15 months, including two courses of actidione, failed to produce any significant change in the course of the disease, death finally resulting from the obstructive complications of basilar meningitis. At necropsy viable Coccidioides immitis organisms were present.

The onset of illness due to C. immitis was never accurately determined in the third case, although during both the years preceding the appearance of the disseminated form of the disease

he had suffered febrile illnesses of the respiratory tract, while living in southern California. Involvement of the meninges was demonstrated on admission to the hospital; but while he was under observation further dissemination occurred, hematogenous in type, as illustrated by the appearance of miliary pulmonary infiltration and by the necropsy findings.

The original infection in the fourth case was a relatively mild chest cold, which appeared while the patient was working in western Texas. It was followed almost immediately by meningitis. He was thought to have tuberculous meningitis and received streptomycin therapy. Even at necropsy the condition was thought to be tuberculosis, and cultural studies for coccidioidomycosis were not done. The microscopic sections, however, revealed the coccidioidal organisms, and no acid-fast organisms could be demonstrated. Serologic studies and skin testing with coccidioidin would undoubtedly have clarified the diagnosis.

While one patient apparently underwent remission after the use of actidione, the authors could not evaluate the effectiveness of this antibiotic from this study. They stress the importance of considering coccidioidomycosis in the diagnosis of chronic meningitis.

ALPERS, Philadelphia.

SUBACUTE BACTERIAL ENDOCARDITIS PRESENTING AS A SUBARACHNOID HEMORRHAGE: REPORT OF A CASE WITH RECOVERY. R. L. WHIPPLE, Ann. Int. Med. **35**:1351 (Dec.) 1951.

The incidence of subacute bacterial endocarditis complicated by subarachnoid hemorrhage reported in the recent medical literature is low. However, an incidence of subarachnoid hemorrhage of approximately 5% in a series of 44 cases of bacterial endocarditis, as reported by Paul, Bland, and White, suggests that it occurs more frequently than is recorded.

Whipple describes the case of a man aged 41 in which the diagnosis of subarachnoid hemorrhage resulting from a mycotic aneurysm secondary to subacute bacterial endocarditis was suspected on admission because of the history and findings of heart murmur, splenomegaly, petechiae, stiff neck, left hemiparesis, and bloody spinal fluid. There was an interval of eight days between the time of admission and the beginning of therapy because of the time required for culturing and identifying the infecting organism, which proved to be alpha hemolytic Streptococcus.

Penicillin was begun with a daily dose of 300,000 units. The initial course of therapy with penicillin produced marked subjective and clinical improvement, with clearing of the symptoms and signs referable to the central nervous system, as well as the symptoms and signs of subacute bacterial endocarditis, except for the persistence of splenomegaly and heart murmur. Subsequently, however, the patient had three relapses, and only by an increase in the daily dose of penicillin to 400,000 units over a period of 30 days did cure of the subacute bacterial endocarditis result. Final cure was not obtained until some seven months after the subarachnoid hemorrhage, and approximately one year after the onset of symptoms of subacute bacterial endocarditis. When seen four years after his last course of penicillin, the patient remained well and had no cardiac limitations in regard to his activity.

Whipple believes that recovery in this case was due to the fact that, fortunately, the site of the mycotic aneurysm, with rupture and subarachnoid hemorrhage, was a minute branch of the right middle cerebral artery supplying the motor cortical area. The chances of recovery seem to depend on the size and location of the cerebral artery involved, and adequate penicillin therapy is necessary to cure the subacute bacterial endocarditis. He suggests that any patient who presents cerebral symptoms, heart murmur, fever with or without splenomegaly, and petechiae should be suspected of having subacute bacterial endocarditis.

ALPERS, Philadelphia.

SWINEHERD'S DISEASE (ASEPTIC MENINGITIS) DUE TO LEPTOSPIRA POMONA. J. H. COFFEY, J. DRAVIN, and W. C. DINE, J. A. M. A. **147**:949 (Nov. 3) 1951.

In this country it has been customary to think of leptospirosis only in the form of Weil's disease (spirochetal jaundice), producing severe liver damage with jaundice and causing a high mortality. Current studies indicate that other leptospiras, particularly Leptospira pomona, associated in nature principally with hogs and cattle, frequently produce a mild systemic infection, with aseptic meningitis as the predominant syndrome. The leptospiras are not easily isolated in

such cases unless examination is made very early, but in nearly all cases high titers are found when leptospiral agglutination tests are run on serum specimens in the acute or the convalescent stage.

Iridocyclitis may occur as a late sequel to acute systemic leptospiral infection, the interval between the initial infection and the ocular inflammation varying from three weeks to one year, but being most commonly four to eight months. Penicillin has been found valuable in the treatment of Weil's disease and in these cases.

The authors describe a patient aged 27, a cattle herder, who had had fever, headache, chills, and generalized aches and pains for one week. He had received penicillin the day after onset of the illness. After this the fever and chills cleared, but the headache, dizziness, nausea, and occasional vomiting continued. Physical examination, including neurologic tests, revealed nothing abnormal.

The spinal fluid was cloudy, with 980 cells per cubic millimeter, 86% of which were lymphocytes and 14% neutrophiles. The protein content was 98 mg. per 100 cc., and the initial pressure, 280 mm. of water.

The headache cleared one week after onset, and the patient became asymptomatic. The spinal fluid findings did not become normal until six weeks after onset of the illness. Several serum specimens were found positive for leptospirosis at diagnostic titers by both complement-fixation and agglutination tests. The specific organism was Lept. pomona.

The authors point out that as more agglutination tests for Lept. pomona are done in cases of iridocyclitis, aseptic meningitis, and influenza-like diseases, this pathogen will probably be found to be more frequent and widespread than has heretofore been believed.

ALPERS, Philadelphia.

TREATMENT OF MENINGITIS BY INTRACISTERNAL INJECTION OF CHLORAMPHENICOL. O. TRINIDADE and F. NASTARI, J. A. M. A. **147**:1757 (Dec. 29) 1951.

The case reported here is interesting not only because it concerns an uncommon disease—meningitis due to Shigella paradysenteriae—but also because it suggests another route for the administration of chloramphenicol to patients.

The patient, a man aged 22, was operated on for acute appendicitis with the use of spinal anesthesia. The appendix was ruptured during operation. The cerebrospinal fluid obtained by lumbar puncture at this time was clear. The day after operation symptoms of meningitis appeared, and cloudy spinal fluid was obtained 24 hours later. Penicillin and streptomycin were given cisternally until the 11th day, with failure of the fluid to clear and with the clinical picture becoming progressively worse. At this time culture of the first cisternal-fluid specimen revealed the causative agent to be S. paradysenteriae. Penicillin and streptomycin were discontinued, and oral administration of chloramphenicol was begun. From the 11th to the 18th day the patient received a total of 20.5 gm. of the drug by mouth.

In spite of the administration of chloramphenicol, the patient showed little improvement on the 12th day. At this time a "loading" dose of 62.5 mg. of chloramphenicol was administered intracisternally, with excellent results. The following day this dose was repeated. The patient continued to improve, and 48 hours later the spinal fluid was clear, containing only 16 cells per cubic centimeter.

The patient was discharged on the 37th day, fully recovered, without neurologic sequelae. On reexamination after three months he was clinically well and the cisternal fluid was clear.

The authors attribute this patient's recovery principally to the intracisternal administration of chloramphenicol. They recommend this route of administration because the antibiotic can be easily sterilized by boiling and possesses low toxicity.

ALPERS, Philadelphia.

EXTRADURAL CEREBELLAR HEMATOMAS. R. A. MUNSLOW, J. Neurosurg. **8**:542 (Sept.) 1951.

Extradural hematoma is a lesion almost universally resulting in fatality when not attacked surgically. The symptom complex of such lesions occurring above the tentorium is generally well recognized and treated. However, only seven cases were found in the literature in which extradural hematoma occurring below the tentorium had been recognized and cured.

Two such cases occurring without localizing cerebellar signs prompted this report. Both cases terminated fatally, one without operation and the second 24 hours after operation.

Head trauma, particularly a blow to the occiput, usually initiates the lesion. The probable mechanism of injury is a laceration of some portion of the lateral sinus, with subsequent escape of blood downward into the potential epidural space of the cerebellar fossa. A fracture line will generally be found crossing the lacerated sinus. The extradural clots may be formed acutely or may accumulate more slowly.

Munslow advises that, given a patient who has sustained trauma to the occiput and complains of headache, suboccipital pain and vomiting, who has an occipital fracture, and who exhibits stiff neck, drowsiness, and irritability, exploratory perforator openings should be placed over the cerebellum, whereby an extradural clot may be detected. Should a clot be uncovered, the incision can be enlarged and craniectomy carried out until the source of bleeding is identified and controlled. Though a normal extradural space may be disclosed in the majority of cases, in the rare case in which such a clot is encountered the patient will be saved from irreversible respiratory failure.

ALPERS, Philadelphia.

ARTERIOVENOUS ANGIOMAS OF THE BRAIN. EGAS MONIZ, Arq. neuro-psiquiat. **9**:303 (Dec.) 1951.

A married woman aged 38 became hemiplegic over a period of 18 hours after an attack of typhoid. Before the hemiplegia developed, she had severe pain in the left hip region for a short time. Convulsions appeared soon afterward, beginning on the left side and ending in unconsciousness and generalized seizures. For 15 days before admission she had ideas of persecution and auditory hallucinations. The angiograms showed a large angioma in the right frontoparietal region. The dye immediately outlined the superior longitudinal sinus, indicating a direct connection between the arterial anomaly and the sinus. A similar arterial connection was found in the author's series of angiograms at the Hospital Santa Marta. Olivecrona reported a similar case.

The hemiplegia is probably due to a hemorrhage in the region of the angioma. The convulsions are more probably the result of spasms with hypoxia in the same region. The mental changes, such as this patient showed, are extremely rare. The author has never seen them in his series of angiomas. In three of Olivecrona's cases, published by Norlén, there were mild mental changes. Norlén noted that the blood vessels even far from the angioma often filled poorly, indicating probable widespread impairment of circulation. The author thinks that these widespread circulatory changes are the cause of the paranoid hallucinatory syndrome which this patient presented. The hip pain is ascribed to the ischemia of the lobe. Olivecrona, in 1932, was the first one surgically to extirpate a cerebral angioma. Bergstrand and Tönnis, in 1936, reported five cases in which the angioma was completely removed surgically.

N. SAVITSKY, New York.

ACUTE AND CHRONIC EPIDURITIS. T. INSAUSTI and R. F. MATERA, Arq. neuro-psiquiat. **9**:324 (Dec.) 1951.

The authors report six cases of epidural infection, three acute and three chronic. These were associated with a history of pyogenic infection in some other part of the body. In each case the epidural infection was always by way of the blood stream. In no case was there extension to the epidural space of a contiguous inflammatory process. The involvement of the cord itself is oftener the cause of disability in the acute cases than is compression by an epidural abscess. In the chronic cases compression alone usually accounts for the disability. In the chronic cases pyramidal-tract degeneration due to compression alone is found. In acute cases with myelitic involvement there is more frequently spastic paralysis; flaccid paralysis is commoner in the chronic cases. The authors call attention to the peculiar fringed appearance of the inferior end of the myelographic column at the site of block. In all cases of this infection the authors advise against puncture into the epidural space at the level of infection because of the danger of spreading the infection. They do not agree with those who believe that the prognosis of chronic epidural infection is better than that of the acute type. One of the patients with acute infection made a complete recovery after operation. One died, in shock, 40 hours after the operation, and the third recovered only incompletely. Of the three patients with the chronic

form, one died a week after the operation, of pulmonary tuberculosis. The second was removed by the family soon after operation, so follow-up observation was impossible. The third showed no improvement of motor, sensory, or sphincteric defects after operation. The authors urge early diagnosis before evidence of involvement of the cord. Antibiotic therapy is usually given before, during, and after the operation. A multiperforated catheter is advised. It is placed into the epidural space five or six days after operation, or until the fever subsides and the sedimentation rate returns to normal. Instillation of 6,000 units of penicillin is done every six hours through the catheter.

N. SAVITSKY, New York.

Diseases of the Brain

VARIABILITY OF SIGNS IN MULTIPLE SCLEROSIS. I. C. SHERMAN, Ann. Int. Med. **35**:1329 (Dec.) 1951.

Sherman presents a critical method of objective evaluation of the fluctuation of signs in multiple sclerosis. A group of 42 patients were observed in the hospital for three weeks, and the clinical status at discharge was compared with that on admission. Of 466 pathologic signs noted on admission, 69, scattered among 32 patients, showed improvement; at the same time, 39 signs of progression occurred among 30 patients. Comparison of the initial and the final examinations of 23 of the 42 patients who were observed for a long period revealed that of 265 pathologic signs at the onset, 66, scattered among 21 patients, showed improvement and 58, appearing in 19 patients, had progressed.

A more detailed analysis of the signs which varied in frequency or intensity was permitted by a study of the repeated examinations during the course of the illness in 23 patients, who were observed for from 3 to 30 months. The most variable were cerebellar signs, ankle clonus, Hoffmann's sign, nystagmus, and bladder disorders. All other signs fluctuated at one time or another except for speech. There also appeared several instances of the acute episodic neurologic disorder so familiar in multiple sclerosis.

This study reiterates what has been accepted as one of the diagnostic criteria for multiple sclerosis, namely, its episodic and recurrent nature in some cases. The author also calls attention to the fact that there may be variability in the objective signs without the appearance of any gross episodic disorders.

ALPERS, Philadelphia.

DIAGNOSIS OF CARCINOMA OF THE PITUITARY GLAND. A. B. King, Bull. Johns Hopkins Hosp. **89**: 339 (Nov.) 1951.

Among the characteristic clinical manifestations of pituitary adenomas are bitemporal defects of the visual fields, primary optic atrophy, headaches, and disturbances of growth and metabolism. An alteration of the sella turcica may be demonstrated by x-ray examination. The vast majority of neoplasms of the pituitary are benign and spread along paths of least resistance or expand the sella by pressure erosion. Since the fifth cranial nerve is separated from the pituitary gland by the bony walls of the sella, the cavernous sinus, the carotid artery, and several other cranial nerves, it is rarely involved by pituitary tumors. However, there are certain cases in which pain in the face due to irritation of branches of the fifth nerve may be the presenting symptom, and this type of onset is especially characteristic of a carcinomatous process arising in the pituitary gland. Under these conditions, the neoplasm shows much greater powers of invasion than do the benign adenomas, and the neoplasm may infiltrate for long distances before symptoms due to mass alone present themselves.

King describes a case which he considers one of carcinoma of the pituitary gland, occurring in a woman of 70, in which facial pain was the predominant symptom.

The widespread invasion by the neoplasm with disregard for the usual anatomical barriers, the absence of any capsule, the histologic picture of the individual cells, and the rapid progression of symptoms, all seem to him to point to the diagnosis of carcinoma. The only factor missing is that of metastases, which some authors consider necessary for the diagnosis. King thinks it quite possible that patients with cancer of the pituitary succumb to the intracranial complications before they have lived long enough for metastases to develop.

The presence of facial pain, along with clinical and x-ray evidence of a pituitary tumor, strongly suggests that the neoplasm is a carcinoma. This is especially true when the pain is an early manifestation, because a benign adenoma usually extends in directions other than through the cavernous sinus, whereas a highly invasive neoplasm may reach the fifth nerve by destruction and penetration of the surrounding structures, while exerting insufficient pressure on the other cranial nerves to cause loss of function.

Treatment of carcinoma of the pituitary is still far from standardized. An adequate biopsy would appear to be the first prerequisite for diagnosis. Craniotomy to decompress the optic nerves and adjacent structures should be carried out. Then intensive x-ray therapy may be applied after the tumor has been found to be of pituitary origin.

In the case reported, operative treatment was directed along two ways; one was an attempt to decompress the right optic nerve, in the hope that vision might return, and the other was section of the fifth nerve to alleviate pain. The neoplasm was much too large for complete surgical removal. Unfortunately, the operative approach required to decompress the second nerve and to cut the fifth nerve at the same sitting is extensive, and in this instance was not tolerated by the patient. The postoperative course was very stormy, and the patient died on the seventh day.

ALPERS, Philadelphia.

ORGANIC NEUROLOGICAL SYNDROMES DIAGNOSED AS FUNCTIONAL DISORDERS. M. J. TISSENBAUM, H. M. HARTER, and A. P. FRIEDMAN, J. A. M. A. **147**:1519 (Dec. 15) 1951.

This paper is a plea for a closer working relation between psychiatry and neurology. The need to view the patient as a whole, to interrelate physical and psychiatric problems and to make multiple examinations, as well as the necessity for a reasonable competence in neurology, is stressed.

A total of 395 neurological cases were reviewed. In 342 cases a correct diagnosis was made early in the course of the syndrome. However, in 53 cases (13.4%) the syndrome was incorrectly diagnosed for various lengths of time prior to an eventual change to a definitive neurological diagnosis. In the largest number of cases the disorder was considered functional for two to six years before a change in diagnosis was made.

Parkinson's syndrome, multiple sclerosis, expanding lesions of the brain, and herniated disk, of the commoner neurological syndromes reviewed, showed the highest percentage of cases in which the disturbance was considered to be functional prior to clarification of the diagnosis.

The authors feel that all patients should have a neurological survey before acceptance of psychotherapy, in order that organic disease should be ruled out or established. When neurological disease is suspected, though psychotherapy may be in progress, patients should be reexamined at regular intervals. Psychotherapy, when indicated for neurological cases, can be more definitive, since more precise knowledge would be available as to which part of the picture is organic and which psychogenic.

ALPERS, Philadelphia.

MORGAGNI'S SYNDROME AND BRAIN TUMORS. S. MOORE, J. Neurosurg. **8**:480 (Sept.) 1951.

From a survey of 627 women and 55 men who had hyperostosis and a group of 450 women and 623 men who served as controls, Moore found that for the women the incidence of intracranial tumors in the hyperostotic patients was 6.22% and that in the controls, 6.14%. For the men the corresponding values were 2.27%, and 7.86%.

Except for the meningeal fibroblastoma, there is no significant relation between hyperostosis and intracranial neoplasm. The disparity in the incidence of this tumor in the sexes is impressive. Symptoms of tumor and of hyperostosis are often indistinguishable. Moore holds that it is better to operate and find no tumor than to miss a possible intracranial neoplasm.

ALPERS, Philadelphia.

MASSIVE CEREBRAL INFARCTION PRODUCING VENTRICULOGRAPHIC CHANGES SUGGESTING A BRAIN TUMOR. A. B. KING, J. Neurosurg. **8**:536 (Sept.) 1951.

Thrombosis of intracranial arteries is not ordinarily associated with a rise in intracranial pressure. Edema and swelling may occur with cerebral softening for a time, but usually these lesions do not produce symptoms of intracranial pressure.

The case presented by King illustrates how an extensive thrombotic softening with swelling of the necrotic tissues may mimic a tumor. The patient had sustained a thrombosis of the right internal carotid artery, together with complete occlusion of the anterior and middle cerebral systems on the same side. The arteriographic and ventriculographic changes are presented, and the difficulties in making a differential diagnosis are discussed.

Because of the strong suspicion of an intracranial neoplasm, operation was decided upon. The patient survived 48 hours. Necropsy disclosed only thrombosis and necrosis. There was no evidence of a neoplasm.

ALPERS, Philadelphia.

INFESTATION OF THE HUMAN BRAIN WITH COENURUS CEREBRALIS. B. J. P. BECKER and S. JACOBSON, Lancet **2**:1202 (Dec. 29) 1951.

This is the fourth case of human infection with Coenurus cerebralis, the larval form of the tapeworm Multiceps multiceps. A man aged 28 was born and lived in the Transvaal, in an area where there were sheep, goats, monkeys, jackals, baboons, and vervets. He noticed unsteadiness of his legs and occasional episodes of double vision; then he experienced severe occipital headaches, radiating down the back of his neck to his shoulders and severe attacks of vomiting. Examination revealed nuchal rigidity, early papilledema, slight ataxia of the left arm and leg, and staggering to the left. Ventriculography revealed some dilatation of the lateral ventricles and considerable dilatation of the fourth ventricle. Exploration of the posterior fossa revealed a collection of closely packed cysts around the right accessory (eleventh cranial) nerve and a large cyst at the dilated foramen of Magendie. A second operation was required for relief of tense swelling over the decompression site; nuchal rigidity and numerous cysts were found in the fourth ventricle, together with severe ependymitis in the roof of the fourth ventricle. The cysts contained numerous scolices, each carrying a rostellum armed with two rows of hooklets. Several of the cysts were sterile.

MADOW, Philadelphia.

MENINGIOMA IN THE CEREBELLOPONTINE ANGLE—CONTRALATERAL TRIGEMINAL NEURALGIA: DIAGNOSTIC VALUE OF VESTIBULAR TESTS AND STUDIES OF THE SKULL. J. C. CHARBONNEL and F. BARON, Rev. oto-neuro-ophthal. **23**:46 (Nov.-Dec.) 1951.

A single woman aged 22 complained of burning pains on the left side of the face and mouth for a few months. Later there appeared headaches and some unsteadiness in gait and position. On her admission to the hospital the findings were diminished sensation in the distribution of the right trigeminal nerve, diminution of the right corneal reflex, veering to the left in walking and during the Romberg test, horizontal and vertical nystagmus, upward drift of the outstretched upper extremities, and bilateral choked disk without diminution of visual acuity. There was no gross hearing defect but mild diminution of auditory acuity was noted on audiometric examination; there was total caloric inexcitability on the left side; the responses to the rotation test, however, were equal on the two sides. A roentgenogram of the skull showed widening of the left internal auditory meatus with abnormal increased density of the whole petrous bone on that side. Two months after she was first seen, cerebellar signs and left-sided deafness appeared. A meningioma, the size of a large apricot, was completely removed from the cerebellopontine angle.

The diagnosis of meningioma, rather than of acoustic neuroma, was made because of an intact cochlea with absence of vestibular response and with hyperostosis of the petrous bone on the side of the widened porus acousticus. The unsteadiness without vertigo, and the absence of vestibular response with intact response to rotation suggested central vestibular changes. The upward nystagmus also indicated pressure on the brain stem. The authors considered the involvement of the contralateral fifth cranial nerve as due to pressure on the sensory nucleus of the fifth cranial nerve on the opposite side of the brain stem. The sensory complaints in the distribution of the right trigeminal nerve suggested disease within the brain stem, rather than involvement of the peripheral nerve.

N. SAVITSKY, New York.

EPILEPTIC EQUIVALENTS IN TUBEROUS SCLEROSIS. C. RADLINGER and H. DEMEL, Wien. klin. Wchnschr. **61**:747 (Oct. 28) 1949.

A woman had a history of typical dermatologic manifestations since the age of 10 years, poor vocational adjustment due to low intelligence, and great emotional instability. At the age

of 17, over a period of six weeks, she was depressed and mute, locked herself in her room, remained in bed, and refused food intermittently. There was no history of grand or petit mal. At the age of 34 the patient had an episode lasting eight days during which she left home and wandered aimlessly about the countryside; she had only a vague recollection of this incident. At the age of 36 she disappeared again and when found had walked about 200 kilometers, again in a dream-like state. There was a similar episode six months later. The patient was hospitalized a few months later, after she had burned all her and her mother's clothing after a depressive episode. She showed typical facial lesions of tuberous sclerosis, as well as subungual fibromas. The neurologic status was normal. A roentgenogram of the skull and a pneumoencephalogram were within normal limits. The electroencephalogram showed diffuse mild changes of the alpha waves, which became more pronounced on hyperventilation. Psychologic tests showed a mental age of 13 years. Other members of the family were affected with tuberous sclerosis.

MASON, New York.

Diseases of the Spinal Cord

ELECTROCARDIOGRAPHIC CHANGES IN POLIOMYELITIS: ANALYSIS OF 150 CASES. M. P. MANNING and P. N. G. YU, Am. J. M. Sc. **226**:658 (Dec.) 1951.

The authors studied 150 cases of acute poliomyelitis occurring in children and adults. In 116 of these cases abnormal electrocardiograms appeared at some time during their disease. The commonest findings were, in order of frequency, abnormal T waves, tachycardia, and abnormal Q-T_c duration. Various arrhythmias, prolonged P-R interval, low-voltage QRS complex, and changes in the RS-T segment appeared transiently and were less frequent. Abnormal T waves usually occurred early, and prolonged Q-T_c persisted the longest.

The incidence of abnormal electrocardiographic changes was higher in adults than in children, and in patients with bulbar or high cervical paralysis than in those with lesions in other areas. No significant correlation could be demonstrated between the electrocardiographic abnormalities and the duration of fever or severity of paralysis.

Potassium studies were done in 81 cases and were normal in 70. In only two of the cases with serum potassium levels over 6 mEq., did high-peaked T waves appear in the precordial leads V_{1-3}.

Histologic examination showed evidence of myocarditis in two of the eight fatal cases. Pulmonary complications and dilatation of the right ventricle were present in more than half the cases in which necropsy was performed. The high incidence of pulmonary edema in the fatal cases of acute poliomyelitis was also noted.

Although the incidence of electrocardiographic abnormalities during the course of acute poliomyelitis was high, the authors considered all the changes to be nonspecific. In the majority of patients the abnormal changes appeared and reverted to normal within the first four weeks. A small number of patients still showed abnormalities several months after the onset of disease.

ALPERS, Philadelphia.

COMPRESSION OF SPINAL CORD BY OSTEITIS DEFORMANS (PAGET'S DISEASE), GIANT-CELL TUMOR AND POLYOSTOTIC FIBROUS DYSPLASIA (ALBRIGHT'S SYNDROME) OF VERTEBRAE: REPORT OF FOUR CASES. P. TENG, S. W. GROSS and C. M. NEWMAN, J. Neurosurg. **8**:482 (Sept.) 1951.

Compression of the spinal cord by a lesion of a vertebra is oftenest the result of traumatic injury, metastatic carcinoma, infiltrating sarcoma, tuberculous spondylitis, pyogenic osteomyelitis, osteoarthritis, infiltrating leukemia, or multiple myeloma. Primary osteogenic sarcoma and benign neoplasms of the spine rarely cause compression of the spinal cord. Although osteitis deformans (Paget's disease) is not an uncommon disease and frequently involves the spine, it rarely causes compression of the spinal cord. Polyostotic fibrous dysplasia is a rare bone disease which scarcely ever affects the vertebrae and has never before been recorded as involving the spinal cord.

Teng and his colleagues report a case of Paget's disease of the vertebrae with spinal-cord compression at the first and second thoracic segments in which laminectomy was of benefit; two

cases of giant-cell tumor of the vertebra, one with involvement of the cauda equina and the other with compression of the cord, in both of which complete recovery followed laminectomy, and a case of polyostotic fibrous dysplasia involving the thoracic portion of the spine and causing paraplegia, in which laminectomy was also followed by recovery.

ALPERS, Philadelphia.

LUMBAR AND SACRAL CYSTS CAUSING PAIN. F. SCHREIBER and B. HADDAD, J. Neurosurg. **8**:504 (Sept.) 1951.

In about 1 of each 100 patients operated upon after a diagnosis of rupture of a low lumbar disk is made, Schreiber and Haddad have found a lumbar or sacral cyst. These cysts are fluid-filled swellings within the nerve; they arise from the dura as meningoceles and compress a caudal filament or a nerve tract as it emerges from the dura.

The authors describe three cases. The first represents the immediate effect of injury (swelling); the second, the intermediate stage (hemorrhage into the nerve, with operation several days after the onset of acute symptoms and years after trauma) and the third, the final stage, that of intraneural cyst. It is pointed out that injury to the dura or nerve sheath may occur at operation and be the precipitating factor in the formation of a postoperative cyst. They describe a case in which this occurred.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

SYPHILITIC WRIST-DROP. K. W. G. HEATHFIELD and J. W. A. TURNER, Lancet **2**:566-569 (Sept. 29) 1951.

Heathfield and Turner report two cases of progressive unilateral wrist and finger drop due to neurosyphilis. In the first case, a man aged 43 gave a history of progressive involvement of the posterior (dorsal) interosseous nerve, shown by difficulty in extending the left middle finger, the ring finger, and the little finger. Examination revealed weakness of the extensors of the left wrist and the long extensors of the left thumb and only a flicker of movement in the extensors of the middle, ring, and little fingers of the left hand. The deep reflexes were brisker on the left than on the right. Serologic reactions of the blood and spinal fluid were both positive. He was treated with penicillin, potassium iodide, and a bismuth preparation. Eventually, his condition became stationary.

In the second case, a man aged 61 also had weakness of extension of the middle and ring fingers. Examination revealed wasting of the left forearm in both extensor and flexor groups, weakness of the extensors of the left wrist, and only a flicker of contraction in the extensor indicis proprius. There was an ill-defined area of cutaneous impairment for light touch and pain sensation on the dorsal surface of the hand. The serologic reactions of the blood and spinal fluid were positive, and the patient was treated with penicillin and bismuth.

The authors conclude that although such a condition may superficially resemble a lesion of the posterior interosseous nerve, it is probably syphilitic amyotrophic meningomyelitis.

MADOW, Philadelphia.

CHARCOT JOINTS IN DIABETIC NEUROPATHY. J. LISTER and R. H. MAUDSLEY, Lancet **2**:1110 (Dec. 15) 1951.

The authors report the case of a man who had suffered from diabetes mellitus for two years and then had recurrent attacks of diarrhea and painless swelling of the right foot. The diabetes was first diagnosed when a septic condition of the toe developed on his left foot and he was found to have glycosuria. Neurological examination at that time showed slight tenderness in the calf muscles on pressure and impairment of vibration sense and appreciation of pinprick in the arms and legs; position sense was slow, but accurate. The deep reflexes were absent in all four limbs. The toe had to be amputated, and he continued to complain of increasing weakness of the legs and burning in the feet, despite good control of his diabetes and treatment with thiamine hydrochloride and liver extract over the next two years. There then developed diarrhea and painless swelling of the right foot. No dorsalis pedis pulse could be detected, and the neurological findings were the same as the original ones except that the muscle

tenderness had disappeared and the position sense in the joints of the feet was grossly impaired. Lumbar puncture revealed no cells; the protein was elevated to 70 mg. per 100 cc. The Wassermann and Kahn reactions of the spinal fluid were negative. A roentgenogram of the foot showed necrosis of the cuboid bone and adjacent surfaces of the navicular and lateral cuneiform bones. Despite attempts at medical therapy, the leg became infected and had to be amputated. The anterior tibial artery was almost completely occluded by severe atheroma, and the posterior tibial artery was partially calcified. The posterior tibial nerve showed degenerating fibers with dense endoneurial and perineurial fibrosis. The appearances in the tarsal joints were consistent with repeated trauma and lent support to the diagnosis of Charcot's (neurogenic) arthropathy.

The authors express the belief that the cause was obscure but that the disease may be due to peripheral neuritis combined with autonomic involvement (as evidenced by the diarrhea), as well as circulatory impairment, and they mention the possible use of lumbar sympathectomy in this condition.

MADOW, Philadelphia.

TALIPES CAVUS (FRIEDREICH'S TYPE) IN A CASE OF INJURY TO THE CAUDA EQUINA. M. ANDRÉ-VAN DEEUWEN and M. J. ANDRÉ, Rev. neurol. **81**:656 (Aug.) 1949.

Van Deeuwen and André report the appearance of typical unilateral talipes cavus (Friedreich's type) in a man who was wounded by a bullet that entered the third-fourth lumbar interspace and lodged in the dural sac, without damaging the neighboring vertebrae. Surgical exploration and removal of the bullet also revealed interruption of the third, fourth, and fifth sacral roots on the left and the fourth and fifth sacral roots on the right. The patient had a typical cauda-equina syndrome, with paralysis of both legs below the knees. The condition improved gradually over 4½ years, with residuals in the feet and calf. There were slight residual sexual and urinary difficulties. There was, however, more profound improvement of superficial than of deep sensation, and the authors feel that this is atypical for lesions of the cauda and possibly presupposes some injury to the conus as well. The talipes developed on the right side progressively after the accident.

LEGAULT, Washington, D. C.

Vegetative and Endocrine Systems

AMENORRHEA AND GALACTORRHEA IN PITUITARY ADENOMA. R. TOAFF and A. SADOWSKY, Harefuah **41**:189 (Dec.) 1951.

Chiari, in 1855, and Frommel, in 1882, described the syndrome of amenorrhea and galactorrhea. The authors believe that this syndrome may have various causes. They report two cases in which the cause was a pituitary adenoma.

The first case was that of a woman aged 26 who had had three pregnancies; two terminated in normal deliveries and one in a miscarriage. She was admittted to the hospital with a history of amenorrhea and galactorrhea for two years. Large spots of vitiligo also were found over the body. Examination showed mild obesity, normal blood pressure, normal external genitalia, a small uterus, and atrophic vaginal mucosa. The patient was given diethylstilbestrol, and in two months the galactorrhea stopped. She then began to complain of frontal headache and visual disturbances. Optic atrophy, bitemporal visual field defects, and erosion of the posterior clinoid processes were found. Operation was performed, and a tumor of the pituitary was found. About 3 cc. of this tumor was removed, and the operation was followed by a course of x-ray therapy. She lost weight, and the discharge from the nipples became much less marked. The histological diagnosis was basophilic adenoma.

The second case was that of a Yemenite woman aged 30 with amenorrhea following a miscarriage in the fifth month of her fourth pregnancy. After the miscarriage, which took place 15 months before she was seen, her breasts became full, and milk leaked frequently. She also began to gain weight; the milk coagulated when boiled. The uterus was small and the vaginal mucosa atrophic. Examination showed mild hypochromic anemia, a blood cholesterol of 290 mg. per 100 cc., and basal metabolic rate of 17%. The sella turcica was enlarged, and there was destruction of the floor. The patient failed to cooperate in an examination of the eyes and did not complete the course of x-ray therapy.

Galactorrhea has been described in association with chromophobe adenoma (Berblinger, W.: *Schweiz med. Wchnschr.* **71**:1237, 1941) and in acromegaly (Davidoff, L. M.: *Endocrinology* **10**:461, 1926). Amenorrhea and persistent galactorrhea have never been described before in a case of basophilic adenoma.

N. Savitsky, New York.

Treatment, Neurosurgery

Ligation of Internal Carotid Artery for Aneurysmal Lesions of Circle of Willis. R. C. Bassett and H. H. Gass, J. A. M. A. **147**:842 (Oct. 27) 1951.

The purpose of this report is to present the results of experience at the University of Michigan Hospital with simple ligation of the internal carotid artery in the neck as treatment of aneurysms of the circle of Willis.

The effect of ligation of the internal carotid artery in the neck in 17 cases of saccular aneurysm of the circle of Willis and in 5 cases of carotid artery-cavernous sinus aneurysm is presented. Therapeutic benefit is evaluated in terms of improvement in local or neighborhood symptoms caused directly by the aneurysms. Eleven of 14 patients with saccular aneurysm who showed such symptoms and all the patients with carotid artery-cavernous sinus aneurysm had sustained improvement in these symptoms. The procedure was ultimately tolerated well by at least 15 of the 17 patients with saccular aneurysm and by all the patients with carotid artery-cavernous sinus aneurysm.

The follow-up study of many of these patients is too short to permit conclusions regarding the effect on the life expectancy or the recurrence rate. Ligation of the internal carotid artery alone, however, does not carry with it the additional hazard, emotional trauma, and strain associated with a direct surgical intracranial attack. Such an intracranial approach could be made subsequently if it is indicated by further difficulty, and might then be even less hazardous.

For these reasons, the authors believe that ligation of the internal carotid artery in the neck is usually a rewarding procedure when performed for unruptured infraclinoidal aneurysms of the circle of Willis in patients less than 50 years of age and for carotid artery-cavernous sinus aneurysms.

Alpers, Philadelphia.

Postoperative Survival of Patients with Intracranial Oligodendroglioma with Special Reference to Radical Tumor Removal: A Study of Twenty-Six Patients. G. Horrax and W. Q. Wu, J. Neurosurg. **8**:473 (Sept.) 1951.

Horrax and Wu present 26 cases of histologically verified oligodendrogliomas, with special reference to duration of preoperative symptoms, location of the neoplasm, and postoperative period of survival.

Although in some of the tumors histologic examination showed mitotic figures, they were relatively few. Only one tumor showed abundant mitosis. This occurred in a tumor recurring two years after the original operation. Although oligodendrocytes occasionally grow wild, as they have been observed to do by other investigators, it may be concluded that they are in the main slow-growing, so that every effort should be made to remove them as completely as possible when encountered.

The authors believe that the policy of performing grossly total excisions of all gliomas should be emphasized vigorously. Longer survival periods after radical tumor extirpation are evident from the study of previously reported cases, and this policy is substantiated in the present series by an average postoperative survival period of over seven years.

Alpers, Philadelphia.

Muscular System

Studies in Disorders of Muscle: VI. Is Progressive Muscular Dystrophy an Endocrine or Metabolic Disorder? F. H. Tyler and G. T. Perkoff, A. M. A. Arch. Int. Med. **88**:175 (Aug.) 1951.

More than 30 years ago Timme and others suggested that the pathologic process in progressive muscular dystrophy was primarily endocrine. In initiating a long-term study of this

disorder, Tyler and Perkoff considered it desirable to reevaluate this thesis with the aid of some of the more recently developed, as well as the older, clinical signs and laboratory tests of endocrine function. However, clinical and laboratory studies of a series of patients with progressive muscular dystrophy, 28 with the childhood type and 14 with the facioscapulohumeral type, failed to reveal any evidence to suggest a primary endocrine abnormality in this disease.

In addition to these studies of endocrine function, a number of other determinations related to metabolic processes were carried out. Meldolesi and Stefanutti claimed that there is present in the stools of dystrophic patients greatly increased amounts of urobilin, which fluoresces in sunlight without the addition of zinc ions and is a conjugation product of mesobilifuscin. They named this substance myobilin and suggested that it is derived from myoglobin. The present authors were unable to confirm these conclusions of Meldolesi and his group concerning a grossly disturbed porphyrin metabolism. However, in their opinion, failure to demonstrate an abnormality in pigment does not eliminate the possibility that a primary defect in myoglobin metabolism exists in this disease, particularly since little is known about the metabolism of myoglobin in the normal person.

Other studies, including morphologic studies of the blood, chemical determinations on the blood and serum, and routine urinalyses, did not reveal evidence of a significant abnormality in the blood or the renal system. Abnormalities which have been observed can be accounted for by the decrease in muscle mass present in progressive muscular dystrophy. Finally, the authors emphasize that such negative data do not permit the conclusion that progressive muscular dystrophy is not the result of a metabolic disorder. They also point out the possibility that an abnormality in bone and subcutaneous tissue may be associated with the muscular anomaly of progressive muscular dystrophy.

ALPERS, Philadelphia.

MUSCULAR WASTING OF OBSCURE ORIGIN AND THE THYROID GLAND. K. L. Zierler, Bull. Johns Hopkins Hosp. **89**:263 (Oct.) 1951.

The author observed a group of 10 patients beyond the age of 40 in whom hyperthyroidism was characterized mainly by great wasting of muscles. These patients complained chiefly of anorexia, weakness, and loss of weight. Exophthalmos, thyrotropic eye signs, and goiter were not demonstrable or were not impressive in most cases. However, other signs and symptoms associated with typical hyperthyroidism in younger patients were almost always present, though seldom prominent and sometimes overlooked.

In these older patients the process of aging may modify in some way the response to hyperthyroidism. Zierler suggests, as frank speculation, that the apathetic aspect of these hyperthyroid patients may be owing in part to diminution in secretion of adrenomedullary hormones, despite the fact that the capacity to react with exaggeration to administered epinephrine may be comparable to that of patients with typical hyperthyroidism.

A curious pattern of creatinine metabolism appeared in these patients, characterized by hypocreatinuria, impaired creatine tolerance, and surprisingly trivial spontaneous creatinuria. So consistent was this pattern that it became a useful indication for therapeutic trial. The pattern is known not to be specific; it occurs in myotonic dystrophy and in Addison's disease. However, efforts to demonstrate adrenocortical insufficiency in older patients with hyperthyroidism were unsuccessful. The observations may be explained by assuming that the velocity of synthesis of creatine is depressed in the three clinical states in which this anomalous creatine pattern has been noted.

In four patients the combination of loss of weight, tachycardia, and emotional lability was sufficiently impressive to make hyperthyroidism the most likely diagnosis from the start. In the remaining cases continued observation turned suspicion toward the thyroid. In all 10 patients repeated determination demonstrated elevated basal metabolic rates. In the final analysis, convincing demonstration of hyperthyroidism depended on response to therapy. Rapid recovery of weight and restoration of strength occurred uniformly during administration of strong iodine solution U. S. P. (Lugol's solution) or of propylthiouracil U. S. P. or of both.

ALPERS, Philadelphia.

News and Comment

SAMUEL W. HAMILTON MEMORIAL LECTURE AND AWARD

The American Psychopathological Association has established the Samuel W. Hamilton Memorial Lecture and Award in commemoration of the unique contribution made by Dr. Hamilton to the fields of psychiatry, medicine, and sociology. He was one of the founders of the Association, served a term as president and acted as its secretary for many years. The recipient of the Award will be chosen each year by the Council of the American Psychopathological Association and presented with the Samuel W. Hamilton bronze medal after delivery of the Hamilton Lecture.

Dr. William B. Terhune, chairman of the committee to raise the necessary funds, announced that the contributions received from members of the Association, and also from members of the American Psychiatric Association who participated as sponsors, will perpetuate this yearly Award.

This year the first Award was presented to Clarence P. Oberndorf, M.D., clinical professor of psychiatry at Columbia University, for his distinguished contribution to psychopathology, at the annual meeting of the American Psychopathological Association, held on Saturday, June 7, at the Park Sheraton Hotel, New York. Dr. Oberndorf's lecture was entitled "Function in Psychiatry."

THE NEUROSURGICAL SOCIETY OF AMERICA

The fifth annual meeting of The Neurosurgical Society of America will be held at the Cloister, Sea Island, Ga., Sept. 18-20, 1952. The program includes panel discussions on "Treatment of Vascular Anomalies," "Planned Hypotension in Surgery," and "Clinical Problems as Related to Diagnosis," as well as discussions on "Arteriography Versus Ventriculography in the Diagnosis of Brain Tumors," and "Present Status of Radioactive Isotopes in Brain Tumor Diagnosis." The president is Dr. Joseph F. Dorsey of Boston.

ILLINOIS PSYCHIATRIC SOCIETY

At the last election of officers, on May 24, 1952, the following members of the Illinois Psychiatric Society were elected to office: president, Dr. Jules H. Masserman, Chicago; vice-president, Dr. Alfred P. Bay, Manteno, Ill.; secretary-treasurer, Dr. Edward J. Kelleher, Chicago; councilors, Dr. William H. Haines and Dr. Percival Bailey, Chicago.

DR. WARTENBERG HONORED

Dr. Robert Wartenberg, clinical professor of neurology, University of California School of Medicine, has been elected an honorary member of the Italian Neurological Society.

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Adams, R. Charles (1951), Intravenous Administration of Pentothal Sodium in Combination with Other Anesthetic Agents and Methods, J. Missouri Med. Assn., August.

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